12. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES/ACID AEROSOLS

12.1 INTRODUCTION

A rapidly growing body of epidemiologic data examines relationships between particulate matter (PM) concentrations and human health effects, ranging from respiratory function changes and symptoms to exacerbation of respiratory disease and excess mortality associated with premature death.

The purpose of this chapter is to review the epidemiological evidence relating health effects to exposure to airborne particles. Much new information has appeared since EPA's publication of the 1982 document on Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. Environmental Protection Agency, 1982a), its second Addendum (U.S. Environmental Protection Agency, 1986a), and a later Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989). Information from these previous documents is only concisely considered here to provide background for this chapter and to help form the basis for evaluation of more recent publications.

12.1.1 Definition of Particulate Matter and Measurement Methods

As discussed in Chapter 3, "particulate matter" is the generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a wide range of sizes. Particles originate from a variety of stationary and mobile sources and may be emitted directly or formed in the atmosphere by transformation of gaseous emissions such as sulfur oxides (SO_x), nitrogen oxides NO_x), and volatile organic compounds (VOCs). The chemical and physical properties of PM vary greatly with time, region, meteorology, and source category, thus complicating the assessment of health and welfare effects. Particles in ambient air usually occur in two somewhat overlapping bimodal size distributions: (1) fine (diameter less than 2.5 μm) and (2) coarse (diameter larger than 2.5 μm). The two size fractions tend to have different origins and composition, as discussed in Chapter 3 along with other aspects concerning particle size and atmospheric chemistry.

On July 1, 1987 (Federal Register, 1987), EPA published revisions to the PM NAAQS. The principal revisions in 1987 included replacing TSP as the indicator for the ambient standards with a new indicator that includes only particles with an aerodynamic diameter less than or equal to a nominal 10 μm (PM_{10}).

The choice if PM_{10} as an indicator for the revised standards was based on several key conclusions as summarized below:

(1) Health risks posed by inhaled particles are influenced by both the penetration and deposition of particles in the various regions of the respiratory tract and the biological responses to these deposited materials. Smaller particles penetrate furthest in the respiratory tract. The largest particles are deposited predominantly in the extrathoracic (head) region, with somewhat smaller particles depositing in the tracheobronchial region; still smaller particles can reach the deepest portion of the lung, the pulmonary or alveolar region.

(2) The risks of adverse health effects associated with deposition of typical ambient fine and coarse particles in the thoracic region (tracheobronchial and alveolar deposition) are markedly greater than those associated with deposition in the extrathoracic region. Maximum particle penetration to the thoracic region occurs during oronasal or mouth breathing.

(3) The size-specific indicator for primary standards should represent those particles small enough to penetrate to the thoracic region. The risks of adverse health effects from extrathoracic deposition of typical ambient PM are sufficiently low that particles depositing only in that region can safely be excluded from the indicator.

A variety of PM sampling and measurement methodologies have been used in the epidemiology studies discussed in this chapter. Some studies used earlier measures such as British Smoke (BS), Coefficient of Haze (COHs) and Total Suspended Particulate Matter (TSP). Limitations posed for interpreting epidemiologic studies employing such PM measurement methods are discussed both in U.S. Environmental Protection Agency (1982a, 1986a) and Chapter 4 of this document. Additionally, current measures (i.e., $PM_{2.5}$, PM_{10} and sulfates) used in more recent epidemiology studies are defined and discussed earlier in this document in Chapter 4 (Sampling and Analysis of Particulate Matter). Methodologies for strong acid measurement are also discussed in U.S. Environmental Protection Agency (1989) and in Chapter 4 of this document.

12.1.2 Guidelines for Assessment of Epidemiologic Studies

An important concept of the epidemiologic information assessed here concerns its usefulness in demonstrating cause-effect relationships versus merely establishing associations (which may be non-causal in nature) between PM exposures and various health effects. The interpretation of epidemiologic data as an aid to inferring causal relationships between presumed causal agents and associated effects has been previously discussed by several expert committees or deliberative bodies faced with evaluation of controversial biomedical issues (U.S. Department of Health, Education, and Welfare, 1964; U.S. Senate, 1968). Criteria selected by each for determination of causality included: (1) magnitude of the association; (2) consistency of the association, as evidenced by its repeated observation by different investigators, in different places, circumstances and time; (3) specificity of the association; (4) temporal relationship of the association; (5) coherence of the association in being consistent with other known facts; (6) existence of a biological gradient, for the association; and (7) biological plausibility of the association.

Hill (1965) further noted that strong support for likely causality suggested by an epidemiologic association can be derived from experimental or semi-experimental evidence, where manipulation of the presumed causative agent (its presence or absence, variability in intensity, etc.) also affects the frequency or intensity of the associated effects. Importantly, both Hill (1965) and the above-noted deliberative bodies or expert committees were careful to emphasize that, regardless of the specific set of criteria selected by each, that no one criterion is definitive by itself nor is it necessary that all (except temporal relationship) be fulfilled in order to support a determination of causality. Also, Hill (1965) and several of the expert groups noted that statistical methods alone cannot establish proof of a causal relationship in an association nor does lack of "statistical significance" of an association according to arbitrarily selected probability criteria necessarily negate the possibility of a causal relationship. That is, as stated by the U.S. Surgeon General's Advisory Committee on Smoking and Health (U.S. Department of Health Education and Welfare, 1964): "The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability." Apropos to this, Bates (1992) has more recently emphasized the importance of assessing the overall coherence of epidemiologic findings of both morbidity and mortality effects at varying pollutant concentrations in making judgements about likely causal relationships.

Taking into account the above, the following types of questions were considered in assessing the relative scientific quality of epidemiologic studies reviewed here and to assist in the interpretations of their findings.

(1) Was the quality of the aerometric data used sufficient to allow for meaningful characterization of geographic or temporal differences in study population pollutant exposures in the range(s) of pollutant concentrations evaluated?

(2) Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

(3) Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

(4) Were the statistical analyses used appropriate and properly performed and interpreted, including accurate data handling and transfer during analyses?

(5) Were likely important confounding or covarying factors adequately controlled for or taken into account in the study design and statistical analyses?

(6) Were the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

Few, if any, epidemiologic studies deal with all of the above points in a completely ideal fashion. Nevertheless, these guidelines provide benchmarks for judging the relative quality of various studies and for selecting the best for use in criteria development. Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation to all of the above questions, is beyond the scope of this document. Of most importance for present purposes are those studies which provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for health effects associated with ambient air levels of PM currently likely to be encountered in the United States.

Extensive epidemiologic literature on the effects of occupational exposures to various PM specific components is not reviewed here for several reasons:

(1) Such literature generally deals with effects of exposures to PM chemical species at levels many times higher than those encountered in the ambient air by the general population.

(2) Populations exposed occupationally mainly include healthy adults, self-selected to some extent in terms of being better able to tolerate exposures to PM substances than

more susceptible workers seeking alternative employment or other groups often at special risk among the general public (e.g., the old, the chronically ill, young children, and asthmatics).

(3) Extrapolation of observed occupational exposure-health effects relationships (or lack thereof) to the general public (especially population groups at special risk) could, therefore, be potentially misleading in terms of demonstrating health effects among healthy workers at higher exposure levels than would affect susceptible groups in the general population.

The occupational literature does, however, demonstrate links between acute high level or chronic lower level exposures to many different PM chemical species and a variety of health effects, including: pulmonary function changes; respiratory tract diseases; morphological damage to the respiratory system; and respiratory tract cancers. Some consideration of such literature is provided in Chapter 11 on the toxicology of specific PM constituents as useful to elucidate important points on observed exposure-effect relationships.

12.1.3 Epidemiologic Designs and Strategies

The recent epidemiology studies to be discussed generally fall into four categories:

(1) short-term exposure studies related to acute effects, typically on a time scale of one or a few days;

(2) prospective cohort studies, in which health outcomes for individuals recruited at the same time are followed over a period of time, typically several years;

(3) cross-sectional epidemiology studies comparing at a single point in time the health effects of long term-exposures to air pollution of different populations, typically assuming that exposure has occurred over a time interval of several years;

(4) metaanalyses and other syntheses of research studies.

Different types of studies have differing strengths and weaknesses. One limitation common to all of the above different study designs is that only community-level air pollution information is available, generally from one or a few air monitoring stations used to characterize PM and other air pollution and weather exposures over a city or county. Individual personal exposures are generally unknown. However, the acute studies attempt to relate counts of the number of individuals with a specified health outcome to PM exposures during the day when air pollution was measured in the region or possibly within a few days after such exposure. The

health endpoints reviewed here include death, hospital admissions for respiratory or cardio-pulmonary causes, respiratory symptoms reported in a diary by individuals on a selected panel of people who reside in the region, school absences, and results of standard pulmonary function tests (PFT). Sometimes the health outcome data are divided into demographic subgroups by age, sex, or race. Some studies have also divided the mortality data by primary and contributing causes of death on death certificates, such as respiratory causes or cardio-vascular causes, compared with "control" causes that were believed to have little relation to air pollution.

The strength of acute health effects (short-term exposure-response) studies is that they allow evaluations of a single region or community, comparing the response of a population of individuals on one day with one set of pollution exposures to the response of the same population on another day with a different set of pollution and weather exposures. In general, the daily health effects data should be detrended so that only daily fluctuations in outcome related to daily changes in exposure are evaluated. The detrending includes a variety of techniques to minimize the effects of season and yearly changes in population demographics, as well as control or adjustment for unpredictable variables that may affect health outcome, including weather-related variables and shorter-term random events such as influenza epidemics.

Evidence cited in Chapter 11 suggests that PM or certain PM components may have health effects that are independent of the effects of other criteria pollutants to some extent. However, there does not appear to be any biological marker for distinguishing the full range of PM effects from those of some other air pollutants, since PM does not have a unique chemical characterization and therefore may exhibit a multiplicity of effects. The biological effects or biological interactions resulting from exposure to mixtures of PM and gaseous air pollutants are also not well understood, although it has long been understood that urban and rural airsheds contain such mixtures. The problem of identifying PM effects separately from those of other pollutants using observational data from epidemiology studies is therefore complicated because ambient concentrations of PM may be correlated with those of other pollutants for a variety of reasons. One of two distinct positions may therefore be adopted in interpreting PM epidemiology studies: (1) PM health effects are so thoroughly intertwined with those of other pollutants that PM can serve (at best) as a readily measured index of the total mixture of

pollutants in a region; or (2) due to differences in air pollution mixtures among different communities, and in some cases due to differential time series variations among air pollutants within a region, the effects of PM can be distinguished adequately (albeit not perfectly) from those of gaseous copollutants such as other criteria air pollutants (e.g., CO, O_3, NO_2, etc.). In this chapter we adopt the second point of view: a plausible range of PM effects can be estimated separately from those of of other pollutants by inference, usually depending on statistical analyses of epidemiology data within and between different communities.

Particulate matter effects cannot always be clearly separated from those of other pollutants because of some intrinsic mechanistic factors in observational studies: (1) some gaseous pollutants are precursors of PM components formed as secondary particles; (2) some gaseous pollutants are formed by the same processes that form PM; and (3) weather conditions that affect PM emissions and concentrations at a stationary air monitor are likely to have similar effects on emissions and concentrations of other pollutants. Because of the common causal chains relating PM and other pollutants, it may not be appropriate to describe the PM effects as being "confounded" with those of other pollutants versus distinguishing between possible interactive or independent effects of PM and/or other covarying factors (e.g., copollutants, weather, etc.).

Processes that produce PM may also produce the other pollutants. For example, combustion of fossil fuels used in electrical power generation may produce sulfur dioxide (SO_2) as well as PM, so that emissions of both PM and SO_2 may be high or low at the same time. Moreover, SO_2 may also form atmospheric sulfates, which constitute an important part of fine particle mass in many eastern U.S. cities. Likewise, incomplete combustion of fossil fuels in motor vehicles may directly generate PM and primary pollutants such as carbon monoxide (CO) and nitrogen oxides (NO_x) and indirectly contribute to secondary air pollutants such as ozone (O_3) and nitrates, with nitrates also being a PM component. Weather may be a contributing factor to emissions (e.g., by increasing demand for electric power on very hot summer days or very cold winter days), and meteorological conditions such as inversions also contribute to high concentrations of air pollutants. However, it is important to remember that the potential for confounding of PM effects with weather or other air pollutants does not necessarily mean that confounding actually biased the results in any given study. Confounding must be evaluated on a case-by-case basis. Comparison of estimated PM effects across different communities having

different levels of a potentially confounding factor may help to resolve questions about the role of any given potential confounder. This is discussed in more detail in Section 12.2 below.

Prospective cohort studies follow individuals over an extended period of time. The strength of such studies is that individual risk factors can be accounted for by statistical adjustments or control. Known risk factors for mortality include age, sex, race, occupation, economic status, smoking status, use of alcoholic beverages, and body mass index among others. If the individuals selected are representative of PM exposures across different communities, the effects of individual risk factors can be separated from PM exposure effects. This epidemiologic design also allows (in theory) the evaluation of cumulative exposure to PM over the years, whereas the acute effects study design only allows assessment of effects due to short-term exposure changes. One interesting question is whether there are cumulative effects of chronic PM exposure greater than the sum of daily acute effects, since chronic effects must include short-term effects not subsequently cancelled by short-term improvements. These strengths of prospective cohort studies are greatly reduced if inadequate air pollution measurements are available, so that only crude exposure comparisons across cities or regions can be made.

Population-based studies look only at highly aggregated community health outcomes, such as mortality rates. In some cases, averaging may be advantageous. With no individual-level exposure available, it is only possible to compare different cities by statistical adjustment for demographic and climatological differences and for average differences in levels of air pollutants or other community-wide health risk factors. However, the data for such analyses may be obtained and analyzed relatively easily, and such studies have served a useful historic role in hypothesis generation.

There is still much discussion about the appropriateness of using formal mathematical methods known as "metaanalysis" in research syntheses (Shapiro, 1994). This approach, when applied properly, can provide useful guidance in combining the results of diverse studies. Ultimately, synthesis of the results of the studies reviewed here is clearly desirable, but must be guided by substantive knowledge about the individual studies evaluated. For this reason, important methodological issues that affect pertinent studies are discussed next, followed by evaluation of the studies themselves.

12.2 METHODOLOGICAL CONSIDERATIONS

Studies assessed in this chapter were evaluated for several factors of general importance for interpreting epidemiological studies. These include: (1) exposure measurement errors; (2) misclassification of health outcomes; (3) model specification for acute studies; (4) model specification for chronic studies; (5) covariates and confounders; (6) internal consistency and strength of effects; and (7) plausibility of observed effects. In this section are discussed some methodology issues that more specifically affect the assessment of those PM epidemiology studies evaluated later in this chapter.

12.2.1 Issues in the Analysis of Particulate Matter Epidemiology Studies

There are numerous specific features of epidemiology studies of exposure to airborne particles that largely structure the statistical analyses and interpretation of these studies. Important properties that shape the analyses are: (1) health endpoints typically consist of discrete events in individuals (death, hospital admission for cardiopulmonary symptoms, etc.), although some studies use continuous effects indices such as pulmonary function scores; (2) response variables used in most epidemiology studies consist of the number of discrete events of certain types occurring in a particular community during some interval of time, with a variety of possible endpoints for use in any analysis; (3) individual exposures to air pollution are not typically measured, so that all of the individuals in any study area will be assigned the same air pollution concentration corresponding to the nearest monitor(s) in their community, which is often the only monitor; and (4) since the responses (or effects) to exposure to airborne particle mixtures are very non-specific, relationships between particle exposure and health effects can only be inferred after estimating the contributions of all relevant confounders.

Air pollution studies for particulate matter are usually defined as either *acute* studies or *chronic* studies. Acute studies evaluate effects or responses to changes in air pollution over short intervals of time, typically one day to several days. Chronic studies evaluate effects corresponding to differences in long-term exposure to PM and other air pollutants, usually among different communities. A typical acute study relates changes in the response variable, such as the number of deaths per day for individuals of age at least 65 years, to changes in the PM concentration over the last few days, after adjusting for changes in other variables that affect daily mortality such as temperature and humidity. A typical cross-sectional chronic study

compares annual death rates in a number of cities with different yearly average air pollution concentrations, and adjusts for socioeconomic and demographic differences among cities that may affect mortality rates, such as education, race, and age. Several recent chronic studies used the *prospective cohort study design*. In a prospective cohort study, individuals are recruited into the study and followed over an extended period of time, ideally many years. Even though air pollution is still characterized by community-level measurements in these prospective cohort studies, the individual responses may be adjusted for individual risk factors such as age, cigarette smoking, and possible occupational exposures.

Each kind of PM epidemiology study has certain advantages and disadvantages. Acute studies deal with short-term responses to changes in air pollution concentrations and are not confounded with long-term changes in population demographics, behavior, or changes in exposure distribution, although statistical analyses of long time series may require such adjustments. Also, while all epidemiology studies that use community air monitors face the problem that different individuals in a community may have different individual exposures, it is plausible that average *relative changes* in exposure from one day to the next may be adequately characterized by the relative changes at a single community air monitor. On the other hand, acute studies cannot offer any method for dealing with cumulative or long-term effects of PM exposure, since responses that may be due to months or years of past PM exposures would not necessarily be fully reflected in acute exposure-response associations.

One of the unresolved issues in the analysis of mortality data is the extent of shortening of life (or the prematurity of death) associated with ambient PM exposures. Daily mortality time series are analyzed so as to identify responses to changes in air pollution that have occurred within the last few days. If these acute studies are analyzed correctly, the analysis must necessarily eliminate the longer-term effects that occur over time scales longer than several weeks. Thus, acute studies are necessarily limited in their ability to detect displacement of mortality over periods of time longer than several days. However, several studies have investigated patterns of autocorrelation of mortality over periods of a few days. Significant negative autocorrelations are consistent with the hypothesis that excess mortality on one day may have depleted a pool of potentially susceptible subjects on subsequent days (Spix et al., 1994; Wyzga and Lipfert, 1995b; Cifuentes and Lave, 1996). On the other hand, longer-term

mortality studies provide results which are suggestive of additional chronic effects consistent with excess mortality in which some subjects may die prematurely by one or more years.

In principle, chronic studies should allow the assessment of total health effects, since the effect of PM exposure will includes both the detectable acute responses as well as the cumulative effects that are not detected by an acute study. Thus, chronic studies should, for example, be able to detect any additional chronic PM exposure effects beyond acute exposure mortality displacement effects of a few days or a few weeks (sometimes called "harvesting"). In practice, cross-sectional chronic studies comparing different communities must be adjusted for a wide variety of factors that may affect mortality rates, so that differences in community pollution exposure may be confounded with other differences that affect community mortality rates or other community-based health outcome indices. Prospective cohort studies are less subject to confounding by community-level factors. However, unmeasured differences in individual exposure to PM within a community are not necessarily independent of other individual risk factors and could be confounded with these factors. It may also be hard to obtain long-term individual exposure histories. Since the causes of death that are most often associated with excess PM exposure are in the respiratory and cardiovascular categories, the prospective cohort study design has the potential to be superior to the cross-sectional design in its ability to control for other highly significant individual risk factors such as cigarette smoking and occupational exposure. However, unmeasured or inadequately measured individual risk factors can diminish this advantage.

While different kinds of epidemiology studies have illuminated different aspects of PM exposure, the acute mortality and morbidity studies have provided the strongest and most consistent evidence for health effects from PM exposure. Results have been generally consistent across different studies by different investigators, and the results have been robust to reanalyses using different model specifications and different statistical analysis methods. Because the responses are usually in the form of counts (deaths, hospital admissions), it is convenient to characterize results in terms of relative risks (RR) corresponding to a specific PM increment, say 50 $\mu g/m^3$ PM_{10} or 100 $\mu g/m^3$ TSP. The excess risk (RR - 1) for PM exposure is typically much higher among the elderly than among the entire population, typically 2 or 3 times higher for respiratory causes than for all causes, and typically somewhat higher for cardiovascular causes than for all causes. This pattern is plausible for an air pollutant. There is also some coherence

or qualitative consistency between mortality rates and hospital admission rates, with several times as many daily hospital admissions likely to occur as deaths, especially among the elderly. Evaluation of respiratory function and/or symptom changes in relation to daily PM exposures are also supportive of the potential for acute morbidity effects to occur in response to short-term PM exposures.

Cross-sectional studies also tend to be indicative of PM health effects, but the evidence is less conclusive and the effects of other pollutants cannot be as clearly separated from the PM effects. The prospective cohort studies of adult mortality are also supportive of the results of the acute studies. Quantitative consistency is based on the result that the RR estimates from two of the prospective cohort studies are somewhat larger than the corresponding RR estimates from any of the acute mortality studies, as expected if the prospective cohort studies picked up some additional mortality from cumulative PM exposure not detectable in the acute mortality studies.

In the following subsections are reviewed methodological issues that most strongly affect the structure of the statistical analyses used in the subsequently reviewed PM epidemiology studies and the conclusions that can be drawn from these analyses. Most of these issues involve the specification of the concentration-response or dose-response models. The most important issues are the specification of the models for the effects of PM and other pollutants, and for methods by which the data should be adjusted for weather and for other time trends. One particular concern has been the shape of the concentration-response function for PM, with special attention to a possible PM "threshold" concentration and other nonlinearities. Other important substantive issues are discussed later in the chapter, including the differences in averaging times or lags used in the various acute mortality and morbidity models, the possible differences in health effects between fine particles ($PM_{2.5}$ or smaller) and thoracic coarse particles (PM_{10} - $PM_{2.5}$), and effects of chemical composition or acidity of particles.

12.2.2 A Historical Perspective on Air Pollution Modeling

Daily Time Series Models

The analysis of air pollution time series data has proceeded through three broad phases of analytical strategy over the last several decades. The first phase was largely based on "classical" time series and regression analysis methods. These methods generally assumed that the response variable was approximately normally distributed or could be transformed to approximate a

normally distributed variable (for example, by using the logarithm of the mortality rate or the square root of daily counts). Time series structure was focussed on the autoregressive nature of the response variable, and was addressed either by assuming autoregressive or moving average residuals. A common technique was to adjust the mortality time series for the effects of longer-term trends ("detrending") by subtracting out appropriate moving averages of the response variable, most commonly a 15-day moving average centered on the current day's response (Schimmel, 1978; Mazumdar et al., 1981, 1982; Mazumdar and Sussman, 1983; Ostro, 1984). There was some interest in evaluating other "filters" of the data, or in evaluating detrending in the frequency domain using spectral analysis techniques (Shumway et al., 1983, 1988). Similar analyses of time series of the regression predictors or covariates, such as air pollution concentrations and weather variables, were sometimes also done. These techniques were refined and used extensively in the analyses of the mortality series for the 1958 to 1972 London winters (Schwartz and Marcus, 1986, 1990) that played an important role in the 1986 Criteria Document Addendum and the setting of the 1987 PM_{10} NAAQS.

Since that time there has been a substantial shift in the data analysis paradigm. This second phase of analytical strategy is based on the recognition that the counts of discrete events used as responses (such as daily deaths or hospital admissions) are more appropriately modelled as Poisson variables, and that temporal structure is more appropriately included by modeling correlation structure in covariates and in over-dispersion or random variation in the daily mean number function. These analyses have typically been carried out using recently developed methods for longitudinal analysis of counting data (Zeger and Liang, 1986) which depend on an iterative Generalized Estimating Equation (GEE) approach. Some concerns about the validity of the GEE methods were resolved at the workshop on air pollution mortality sponsored by EPA in November, 1994 and by continuing research in statistical theory and methodology (Samet et al., 1995). Many investigators now believe that the Poisson GEE methods provide reasonable estimates of the effect size or regression coefficients for air pollution and other covariates in correctly specified models. There is also reason to believe that the statistical uncertainty of the effect size estimates is also accurately characterized by GEE methods, whether the uncertainty is characterized by asymptotic standard errors, t-statistics, confidence intervals, or P-values (significance levels). However, other statistical methodologies may also be useful.

A third wave of statistical modeling approach seems to be emerging in which the concentration-response functions and other aspects of model specification are not being restricted to explicit parametric functions defined by the analyst. This approach is based on the fact that there really is not any explicit parametric model for the effects of weather-related variables or air pollution on mortality or hospital admissions. So-called nonparametric regression models allow determination of an empirical relationship between response and predictors. Current implementation of methods such as Local Estimation and Scatterplot Smoothing (LOESS) smoothers and generalized additive models (GAM) allow very detailed exploration of air pollution epidemiology data to derive good-fitting models (Schwartz, 1994g,h). Furthermore, classical visual methods for evaluating regression residuals can sometimes be applied, and global goodness-of-fit statistics for the model allow quantitative assessment.

The nonparametric modeling approach allows fitting and visual checking of different concentration-response models. Unfortunately, there is a considerable loss in the ability to easily compare models for different data sets or subsets of data. For example, in comparing the estimated effects of, say, exposure to 100 $\mu g/m^3$ PM_{10} versus 150 $\mu g/m^3$ PM_{10}, linear models for log-mortality can be compared in terms of the regression coefficients or, in this Chapter, in terms of relative risks (RR) per 50 $\mu g/m^3$ difference. The nonparametric models can also be compared across this range, but current computer program implementations do not allow assessment of the uncertainty of the RR estimate across this range. For linear models, the same RR estimate applies to the comparison of 200 $\mu g/m^3$ PM_{10} versus 150 $\mu g/m^3$ PM_{10}, whereas the RR for each different range of 50 $\mu g/m^3$ must be calculated anew using the nonparametric concentration-response model. Of course, if the response to PM or other predictors really is nonlinear, this may be advantageous. On the other hand, the comparisons of response in different studies, in different cities, and in different years or seasons must be made on a similar case-by-case comparison basis.

Some classes of nonparametric models are really "parametric", such as GAM models that are cubic splines whose parameters are the knots or join points of cubic polynomial segments, and the polynomial coefficients in each segment. These parameters and their statistical uncertainty are generally not accessible to the analyst using current computer implementations.

This is not to say that the statistical analyses should be limited to linear, log-linear, piecewise linear or other simple forms that may not fit the response data. However, it is important to point out that in most cases in which concentration-response or dose-response function models are derived from basic biological principles, the parameters in the function may have a specific biological meaning or interpretation that illuminates some underlying process or mechanism. Conversely, the nonparametric model may fit better than a simple parametric model and illustrate important failures in that model and in assumed mechanisms.

This point is illustrated in detail in Section 12.6.2. The two-dimensional nonparametric surfaces fitted by Samet et al. (1995) to TSP and SO_2 for Philadelphia daily mortality data from 1973 to 1980 differ significantly from the standard additive linear model for TSP and SO_2. Interpretations of the role of copollutants in PM models depend on the joint estimates of regression coefficients in additive linear models for PM with and without copollutants. If the additive linear model does not correctly specify the true relationship between the response, PM index, and the other pollutants or covariates, then these interpretations may not be correct.

Thus, the choice of different statistical models may lead to substantive differences in interpretation. In general, however, use of different models within a wide range of reasonable model specifications has produced generally similar conclusions in most studies, as demonstrated in Section 12.6.3.

Statistical Methods for Population-Based Studies

Linear and nonlinear regression methods are generally used when the response variable is a population-based index of community health, such as the annual death rate in the community, possibly stratified by age and cause of death. Statistical methods are similar to those in other applications of regression models in epidemiology, but the problems of confounding of multiple pollutants and of sociodemographic factors have been addressed explicitly in a variety of ways. If the model is specified as a linear model (typically, logarithm of death rate versus logarithm of air pollutant concentrations) and there are no substantial misspecifications of functional dependence or omission of interaction terms, then confounding of variables is often manifested as collinearity of the variables. Some authors have attempted to deal with collinearity by use of biased estimation techniques, such as ridge regression, but the usual technique is to see whether or not the estimated regression coefficient is substantially changed by the inclusion of other pollutants or other potentially confounding demographic factors. The sensitivity of the effect size estimate is not only an easily understood criteria, it is also technically among the most effective diagnostic criteria for potential confounders (Mickey and Greenland, 1989). For this reason, most investigators usually report the results of multiple models, with and without potential confounders.

Statistical Models for Prospective Cohort Studies

The response variables in prospective cohort studies can be discrete events (death, hospital admission) or continuous measurements (PFT values) in individual subjects. Discrete event analyses can be carried out using methods for binary data such as logistic regression, or methods such as the Cox proportional hazards regression model if time to the event is known. The modelling problems are similar to those encountered in the population-based analyses, particularly the role of confounding and the use of fixed sets of predictors as opposed to data-driven search procedures such as stepwise regression.

12.2.3 Model-Building Strategies for Pollution and Weather Variables

The specification of models relating acute health effects to air pollutants and to other variables or covariates is particularly difficult in the case of PM indices, because of the relative absence of any *a priori* theoretical basis for a concentration-response or dose-response

relationship. The extensive statistical modelling of these relationships has therefore been carried out in a much more exploratory manner than is typical for other environmental pollutants. This has been facilitated computationally by the availability of sophisticated modern statistical curve-fitting procedures that do not require specification of parametric dose-response or concentration-response functions. Selection of variables for analysis is based on substantive hypothesis, however, even if functional specifications are not. Paradoxically, the relative convenience of curve-fitting software programs has failed to illuminate underlying mechanisms or processes. In many applications, the nonparametric relationships between PM and response (e.g., logarithm of expected mortality) has been so nearly linear that a linear model provides almost as good a fit to the data as does the empirical smooth curve. However, in the HEI reanalyses (Samet et al., 1995) of the Philadelphia TSP and SO_2 data which includes the effects of both pollutants, there were significant deviations from a purely additive linear model and more complex models appear to be needed to more fully understand the relationship between response (excess mortality) and air pollution.

The four major approaches to developing statistical relationships have been applied in rather similar ways to air pollutants, to covariates related to weather, and to calendar time as predictor variables for the response (mortality or log mortality). The four general approaches are:

(1) fit a parametric regression model with the predictor variable;

(2) divide the predictor variable into intervals or ranges (deciles, quintiles, quartiles, fixed size intervals, etc.) and use membership in the interval as a categorical or dummy variable predictor;

(3) fit a smooth nonparametric regression model with the predictor variable;

(4) divide the data into subsets by season, year, range of predictor values etc., and fit the above models within each subset.

Fitting Parametric Regression Models

Linear models have most often been used for PM and other pollutants (denoted generically OP). In some applications, a linear model with the logarithmic transform of the pollution variable was used. A piecewise linear function was used by Cifuentes and Lave (1996) and is discussed in more detail in Section 12.6.

Various functions have been used for weather-related variables, including quadratic functions (Li and Roth, 1995) and "absolute deviation" or V-shaped piecewise linear functions of temperature. The relationship of mortality to weather is clearly nonlinear, except possibly within a season (e.g., Schwartz and Marcus, 1990), and linear models are not generally used.

Long-term trends in mortality and hospital admissions are evident in most multi-year studies, and detrending is clearly needed. Linear models with calendar time as the predictor are often used, but recent reanalyses of the Philadelphia data (Schwartz, 1996) suggest that a quadratic model may be more appropriate. Seasonal variations within a year have sometimes been modeled using a Fourier series, that is, a sequence of sine and cosine functions of time of year.

Some parametric models have important causal interpretations. For example, a piecewise linear function of PM with 0 slope for PM below a specified critical concentration c, and positive slope above c, would be interpreted as a model suggesting that there is a "threshold" for PM at concentration c, and that PM concentrations below c pose no risk.

Dividing Predictor Variables into Ranges or Intervals

A number of investigators have recognized the possibility of a nonlinear concentration-response relationship and have attempted to circumvent the problem of identifying the parametric form of the relationship by using the PM or other pollution index as a categorical variable, with values in an interval being indicated by a dummy variable (Schwartz and Dockery, 1992a,b). The usual basis for membership is an empirical quantile classification of the PM index, such as by quartiles or quintiles. This procedure appears to introduce some additional measurement error into an epidemiology modeling problem in which exposure measurement error is already a concern.

Classification of weather-related variables by interval membership has similar advantages and disadvantages. One advantage is that combinations of weather variables for different conditions can be included as simple interaction terms, for example "hot wet day" is included by using the product of indicator variables for "hot" and "wet" as an additional predictor variable. A much more sophisticated approach to grouping weather variables is developed by the construction of "synoptic climatologic classes" (Kalkstein et al., 1995).

Time trends can be similarly coded, with separate indicators for season and for year, and season within year as the product of season and year indicators. Indicator variables for day of the week are also convenient.

Recent developments in statistical software and theory allows the fitting of regression models in which the functional parametric relationship between the response and some or all the predictors may not be specified. One class of smooth nonparametric model, the so-called cubic spline method, involves fitting piecewise cubic functions over certain ranges of the predictor variables, with requirements for continuity of the fitted function at the join points (or knots) and additional global requirements for smoothness of the fitted function as defined by the integrated square of the second derivative of the function over an interval. This method is intrinsically nonlinear and iterative when the join points (analogous to the threshold concentration c in a piecewise linear model) are estimated from the data and are not specified in advance. Other methods, such as kernel-type regression smoothers, may also be used. Examples of nonparametric smoothing were presented by Schwartz (1994g,h). One- and two-dimensional nonparametric regression models with TSP and SO_2 have recently been presented in the Health Effects Institute (Samet et al., 1995) reanalyses of Philadelphia data, and are discussed below in more detail. These models allow much better assessment of nonlinearities in the concentration-response model, but do not allow a convenient basis for comparison of air pollution relationships in different cities or at different times.

Nonparametric regression models may be particularly useful in acute response studies in which the purpose of the model is to eliminate the effects of weather, season, and long-term time trends from assessment of short-term changes in mortality or hospital admissions in response to short-term changes in air pollution. The object is not to get the "right" model for weather, for example, but simply to adjust short-term fluctuations in response for changes in these covariates over time scales longer than a few days.

Dividing the Data into Subsets

This approach is an alternative to using models with all of the data. Subset models are similar to the other models, but without indicator variables or parametric or non parametric detrending to account for the fact that there may be somewhat different relationships between the response and air pollution variables in different subsets of the data set, such as seasonal

differences. Other subset approaches include separate analyses for hot days (Wyzga and Lipfert, 1995b) or for "compliance days" (e.g., for $PM_{10} < 150\ \mu g/m^3$). The use of non-contiguous days in subset analyses may complicate the time-series aspects of the analyses. Since any subset analysis is likely to substantially reduce the number of data points (days of data) in the data set, the statistical significance of any effect is likely to be attenuated in a subset analysis. As shown below, data sets with fewer than about 600 to 800 days of data have relatively low power to detect a statistically significant PM effect even if it exists.

12.2.4 Concentration-Response Models for Particulate Matter

The concentration-response relationship assumed in most of the recent analyses is at least additive (as in "generalized additive models") and often simply linear as well as additive. That is, if E(Y) represents the expected number of deaths per day, or expected number of hospital admissions per day, then the model assumed by most recent studies is generally of the form

$$\log(E(Y)) = XB + s(PM) + S(OP)$$

where s(PM) is a smooth function of the particulate matter index (PM) and S(OP) is another smooth function of the other pollutant(s) in the model. All of the other covariate adjustments are denoted, generically, XB. There has so far been little consideration of piecewise linear models with a join point at concentration PM = c (i.e., a "linear spline"), with the general form:

$$s(PM) = a\ PM \qquad \text{if } PM < c,$$
$$s(PM) = b\ (PM - c) + ac \qquad \text{if } PM > c.$$

A special case is the model with a "threshold" at c, of the form (a = 0):

$$s(PM) = 0 \qquad \text{if } PM < c,$$
$$s(PM) = b\ (PM - c) \qquad \text{if } PM > c.$$

The paper by Cifuentes and Lave (1996) is an informative application of piecewise linear modelling, and is discussed in some detail in Section 12.6. However, as noted in Section 12.2.5,

it is very difficult to distinguish threshold model from other nonlinear models, and such an abrupt nonlinearity may be biologically unrealistic.

Even less work has been done in investigating interaction models among pollutants, which are intrinsically non-additive. These are also discussed in Section 12.6, in connection with the recent Health Effects Institute analyses (Samet et al., 1995) of the relationships between mortality, TSP, and SO_2 in Philadelphia.

Most of the responses or adverse health effects are quantified in this chapter by the term "relative risk" or "risk rate", denoted by RR. This term is used here to denote expected excesses in mortality rates, hospital admissions rates, and so on over baseline levels as a function of specified increments in air pollution. This approach allows comparison of air pollution effects without consideration of baseline differences in rates in different communities with differing socioeconomic properties, different prevalence of illness, or different climate. If the estimated effect of the air pollution exposure is characterized by the regression coefficient denoted b in the above model, then the relative risk RR, for a specified PM increment (denoted PMinc) is:

$$RR = \exp (b\ PMinc).$$

Since most statistical estimates of b also allow a calculated (asymptotic) standard error for *b*, denoted se(b), the lower confidence limit (LCL) and upper confidence limit (UCL) for RR are:

$$LCL = \exp ((b - t\ se(b))\ Pminc),\ UCL = \exp ((b+t\ se(b))\ PMinc).$$

The value of t for a 95 percent confidence interval is about 2. The values of Pminc depend on the PM index: 100 $\mu g/m^3$ for TSP, 50 $\mu g/m^3$ for PM_{10}, 25 $\mu g/m^3$ for $PM_{2.5}$, etc.

An alternative approach to characterizing response to PM involves fitting a somewhat different model. If the concentration response model is fitted in log-log form, as is common for most population-based cross-sectional analyses, then the regression coefficient is often called an elasticity. If the elasticity for PM is denoted k, then the model fitted is usually of the form

$$E(\log(Y)) = XB + k \log (PM)$$

The parameter k can be thought of as the relative change in response per relative change in PM, for example the percentage change expected in Y for a one percent change in PM. The elasticity

k is not directly comparable to a log-linear regression coefficient b. The log-linear form of the model can often be approximately compared by calculating an "elasticity at the mean":

Elasticity at the mean = b (mean of PM) / (Mean of Y).

In general, the elasticity at the mean will not be the same as an estimated k. Lipfert and Wyzga (1995b,c) make extensive use of elasticity as an index of risk.

12.2.5 Modeling Thresholds

The existence of thresholds can be argued both biologically and statistically. The biological arguments have been given by several authors, including Stokinger (1972), Dinman (1972), and Waldron (1974). Methods for estimating threshold models have been given by several authors including Quandt (1958), Hudson (1966), Hasselblad et al. (1976), Crump (1984a,b), Crump and Howe (1985), Cox (1987), and Ulm (1991). However, the concept of a threshold may be confused with the concept of a non-zero background. A threshold model starts out completely flat, possibly above zero, and at some point begins to curve upwards. A non-zero background model begins above zero and continually curves upward. However when fitting data, "... an additive background dose is generally not distinguishable from a threshold" (Cox, 1987). Cox (1987) gives 10 real data sets where thresholds have been estimated, and in every one of them it is possible to fit a non-threshold model which fits nearly as well. Thus, for epidemiologic studies, the question of thresholds may be difficult to resolve because of difficulties in estimation. When there is substantial measurement error in the exposure variable or heterogeneity in threshold values in a population, it may not be possible to identify a threshold using aggregate response data such as mortality counts or hospital admissions.

Many epidemiological studies reviewed in this section were structured to develop linear or log-linear models with no such threshold, and in many cases, this assumption has been supported by the data plots presented. However, it has also been shown that it may be difficult to distinguish among alternative regression models with confidence, presumably because the main outlying observations are controlled by factors not included in the model. In such cases, linear and threshold models may have essentially equivalent predictive power. In any event, the epidemiology studies reviewed in this chapter have limited power to identify or detect thresholds. Biological and mechanistic hypotheses about thresholds have not yet reached the

stage of quantitation. While many of the epidemiology analyses clearly estimate higher risks of effects at higher PM levels than at lower levels, it is currently not feasible to preclude the possibility that such effects may have threshold-like flattening of response in the midrange of current ambient exposures.

The detection of thresholds for health endpoints used in PM epidemiology studies would be technically difficult even if exact biological thresholds existed, for two reasons: (1) intrinsic biological variability; and (2) measurement error in exposure and other covariates. The effect of biological variability may be seen in a conceptual model in which each individual has at any given moment a specific PM exposure concentration which, if exceeded, would kill the person or send him or her to the hospital with specific symptoms. It is likely that the individual's susceptibility to PM is itself changing over time, reflecting disease state and other physiological conditions and environmental stresses, so that a specific PM concentration that might kill the individual at one time would not do so at some other time. Inter-individual differences in susceptibility are also to be expected, in addition to intra-individual variability over time. When individual thresholds are distributed over some range of values, the composite apparent relationship between response and PM concentration would not appear to have a threshold.

The second reason why thresholds would be difficult to detect is that individual PM exposures are not known, so that the use of community PM concentration as a predictor introduces an unknown but possibly large statistical "measurement error". It has long been known that measurement error in regression models can change the apparent shape of a regression model specification, from truly linear to apparently nonlinear as well as from truly nonlinear to apparently linear. This has long been known to statisticians, for example, in a widely cited paper by Cochran (1968), based on a theoretical analysis by Lindley (1947), but is only rarely mentioned in the epidemiology literature (Gilbert, 1984). Lipfert and Wyzga (1995b) have studied some aspects of this using computer simulation methods with piecewise linear threshold models and parameters relevant to TSP mortality studies. Thresholds often become undetectable, even when they really exist and a threshold model is correctly specified, if the predictor is measured with statistical error. Thomas et al. (1993) review other issues associated with measurment error problems.

12.2.6 Confounders and Choice of Covariates

Confounders in epidemiologic analyses must: (1) be an independent risk factor for the outcome; (2) be associated with the exposure variable; and (3) not be an intermediate step in the causal path between the exposure and the outcome (Rothman, 1986). The risk factor need not be causal in this case. Thus, many weather variables, as well as some co-pollutants, may qualify as potential confounders for PM-mortality or morbidity associations.

The causality of various weather and pollution variables may or may not be clear, however. For example, an extreme (hot or cold) temperature is known to cause excess mortality, and laboratory human and animal studies support biologically plausible mechanisms for such observations. Thus, simultaneous inclusion of temperature and pollution variables in a time-series regression is crucial, although there is some chance that this may result in under-estimation of pollution coefficients because temperature is also correlated with meteorological conditions that cause air pollution build-up. Wind speed is clearly a good predictor of air pollution build-up, but is not directly causally related to health outcomes. Therefore, inclusion of wind speed in mortality/morbidity regressions is not recommended for air pollution epidemiology unless it is part of an appropriate combined index of weather patterns. Barometric pressure is an example of another variable whose effect (within the range of day-to-day variation) on physiological functions is not clear (Tromp, 1980). It is associated with certain physiological changes (such as shift in blood pressure), but this may be due to its association with temperature change, which is also related to change in blood pressure. Barometric pressure is also correlated with air pollution levels. Thus, while there is a need to address potential confounders, care must be taken that the regression model selected is not over-specified.

Common air pollution variables, such as SO_2, O_3, NO_2, and CO are all known to cause various types of health effects and physiological changes. However, whether short-term exposures to commonly occurring levels of these pollutants cause premature deaths, independent of PM, is not known. In fact, some of these pollutants may be co-factors, rather than confounders. Possibility of synergistic effects of these pollutants are almost never examined or discussed in the current literature. The fact that PM is not a chemically specific pollution index makes the issue of confounding even more complicated. For example, PM may include sulfates, which are formed from SO_2. Then, SO_2 becomes part of the causal pathway of PM effects, and is no longer a confounder for this PM. Also, if reduction of PM results in reduction of co-pollutants, a PM regression coefficient derived from a multi-pollutant regression model may

give misleading results for policy analysis. In addition, it is unlikely that a mixture of these pollutants affects human health in a simple additive manner. Thus, there is an inherent limitation in the prevailing explanatory multi-pollutant regression approaches.

On a day-to-day basis, the concentrations of these air pollutants, as well as PM, may be correlated to varying degrees, due to the meteorological conditions that control dispersion of these pollutants. Care must therefore be taken when including these correlated pollution variables in a health effect regression, as their coefficients may be unstable. Furthermore, the significance of coefficients for each variable may be influenced by their individual measurement errors, rather than their causal strengths. Thus, without external information regarding differential error and some description of collinearity among the covariates, interpretation of these multiple regressions with collinear variables can be misleading.

Under circumstances where various collinear variables are present and each one of the pollutants is suspected of causality to differing degrees, a single pollutant model may result in over-estimation of the coefficient for that pollutant, while a multiple pollutant model may result in under-estimation of each pollutant's coefficient. Separation of possible effects from these various correlated pollutants may be difficult from a single study, but may be possible by evaluating the consistency of coefficients across studies in which the levels and the extent of collinearity of co-pollutants vary. To facilitate such collective understanding (or even meta-analysis), it is crucial for each study to include systematic description of collinearity among the covariates (e.g., correlation of the estimated parameters), levels of each pollutant, and discussion of biological plausibility for each variable at the observed ambient levels.

While the parsimony of a model is generally desirable, blind reliance on the automatic variable selection schemes based on the F-statistic, such as stepwise regressions, or the use of other criteria, based on residual error and number of parameters (Akaike, 1973; Schwarz, 1978) is not appropriate for epidemiologic purposes, as the objective is not to develop a parsimonious model, but to assess the impact of pollution while adequately 'controlling' for other covariates.

12.2.7 Confounding in Cross-Sectional Analysis

Development of an appropriate regression model for cross-sectional (spatial) analysis is fraught with many of the same difficulties found with time-series (temporal) analyses. The central problem (as in all multiple regressions) is to "identify the true confounders without

overadjusting" (Leviton et al., 1993). With spatial analysis, adjustments must be made for spatially varying factors that affect (or are correlated with) air pollution and that affect longevity. Whereas many factors affect longevity (age, genetics, race, poverty, education, alcohol consumption, water quality, climate, lifestyle, for example), the extent to which any of these factors may be correlated with air quality varies with the scale being considered. In most cases, the intercorrelations are indirect; for example, industrial locations have more air pollution and often the people who live there are on the lower end of the socioeconomic scale. Thus, economic factors may be a confounder because of their additional health risk impacts. Regional air quality trends arise from climatic factors and from the types of fuels and industrial activities present. However, ways of accomplishing "spatial detrending" have not been considered in much detail and it may not be possible to fully disentangle regional air pollution from other regional characteristics; Lipfert (1994a) showed, for example, that SO_4^{2-} was correlated with regional factors while TSP was correlated with local characteristics.

In a prospective cohort study, each individual should be characterized according to relevant demographic and lifestyle attributes, which not only provides control in a multi-variate model but also allows for stratification by attribute. In an ideal situation, the effects of air pollution can then be readily examined by regressing survival against individual air pollution exposures. In population-based (ecological) studies, entire communities are classified or described by these attributes in addition to their average air pollution levels. The regression must then deal with the entire communities rather than individuals, a situation that could give rise to the well-known ecological fallacy. To the extent that both of these types of analyses are forced to use the same types of spatially-averaged air quality data, the differences between them are due to the ways in which they handle the "control" variables. In the absence of interactions among these variables on an individual level, the two types of analyses should produce comparable results.

At present, the selection of appropriate control variables appears to be somewhat more of an art than a science. First, many of them are surrogates for the actual effects on health and longevity. For example, income cannot purchase good health directly but increased income may allow access to better medical care; and more education may not only lead to higher income, it may also allow one to make better use of the resources available. Data on diet, genetic susceptibility, and many lifestyle parameters are not available for individuals or local communities; data on broad regional trends may be available in selected instances. The

determinants of good health may change over time (such as quitting smoking, taking up an exercise program, etc.); using data obtained at entry to a prospective study might later lead to misclassification errors for some participants.

Defining a mortality model requires selecting the appropriate control variables; the various extant cross-sectional studies have devised different ways of accomplishing this. By and large, the prospective studies have been limited to the parameters that were selected at entry to the study, many years ago in most cases. Population-based studies have more flexibility because of the myriad sources of information describing communities, although most of them are surrogates for the real variables that affect health. As pointed out by Ware et al. (1981), "it is likely that the effects of variables such as personal habits, occupational exposure, and medical care cannot be fully quantified in this way. If any of these factors covaries with air pollution levels, a spuriously large effect will be attributed to air pollution." More formally, errors in estimating the true relationships between outcome and confounders will be reflected as artifacts in the observed relationships between outcome and air pollution. Given the diversity of approaches to the problem, some simple caveats arise:

1. Candidate variables should have reasonable expectation of a causal relationship with the outcome, based on exogenous findings. Variables such as elevation or rainfall do not appear to meet this standard, for example, and purely geographic variables such as latitude or region are probably better used to define stratified subsets.

2. Given the implied importance of the "correct" specification of potential confounders, results should be presented for these variables and compared with a priori expectations.

3. Consistency of results with a variety of models, including both optimized (such as stepwise) and defined (forced entry) types, is required to provide confidence in the conclusions.

12.3 HUMAN HEALTH EFFECTS ASSOCIATED WITH SHORT-TERM PARTICULATE MATTER EXPOSURE

Some of the earliest indications that short-term ambient air particulate matter or acid aerosols exposure may be associated with human health effects were derived from the

investigation of historically well-known, major air pollution episode events. These include the Meuse Valley (Belgium), Donora, PA (USA), and London (UK) episodes.

Firket (1931) described the December 1930 fog in the Meuse Valley and the morbidity and mortality related to it. More than 60 persons died from this fog and several hundred suffered respiratory problems, with many of the latter complicated by cardiovascular insufficiency. The mortality rate during the fog was more than 10 times higher than normal. Those persons especially affected were the elderly, those suffering from asthma, heart patients, and other debilitated individuals. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of pollutants in ambient air during the episode are available by which to establish clearly their relative roles in producing the observed health effects, but high PM levels were obviously present.

Schrenk et al. (1949) later reported on the atmospheric pollutants and health effects associated with the Donora smog episode of October 1948. A total of 5,910 persons (or 42.7%) of the Donora population experienced some effect. The air pollutant-laden fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths occurred, 18 of them being attributed to the fog. An extensive investigation by the U.S. Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed across all age groups and, on average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population and was evenly distributed through all age groups. Dyspnea (difficulty in breathing) was the most frequent symptom in the more severely affected, being reported by 12% of the population, with a steep rise as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea. While no single substance could be clearly identified as being responsible for the October 1948 episode, the observed health effects syndrome seemed most likely to have been produced by two or more of the contaminants, i.e., SO_2 and its oxidation products together with PM, as among the more significant highly elevated contaminants present.

Based on the Meuse Valley mortality rate, Firket (1931) estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to the Meuse Valley one occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of 1952, as noted by Martin (1964). During the 1952 fog, evidence of bronchial irritation, dyspnea, bronchospasm

and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners; and a considerable increase in sudden deaths from respiratory and cardiovascular conditions occurred. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute hypoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) reported that in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. It is possible that sulfur trioxide, dissolved as sulfuric acid in fog droplets, appreciably augmented the harmful effects of PM and/or other pollutants.

The occurrence of the above episodes and resulting marked increases in mortality and morbidity associated with acute exposures to very high concentrations of air pollutants (notably including PM and SO_2 in the mix):

(1) left little doubt about causality in regard to the induction of serious health effects by very high concentrations of particle-laden air pollutant mixtures;

(2) stimulated the establishment of air monitoring networks in major urban areas and control measures to reduce air pollution; and

(3) stimulated research to identify key causative agents contributing to urban air pollution effects and to characterize associated exposure-response relationships.

Besides evaluating mortality associated with major episodes, the 1982 criteria document (U.S. Environmental Protection Agency, 1982a) also focused on epidemiology studies of more moderate day-to-day variations in mortality within large cities in relation to PM pollution. Evaluating risks of mortality at lower exposure levels, the 1982 criteria document concluded that studies conducted in London, England by Martin and Bradley (1960) and Martin (1964) yielded useful, credible bases by which to derive conclusions concerning quantitative exposure-effect relationships. The 1986 addendum to the 1982 criteria document (U.S. Environmental Protection Agency, 1986a) also considered several additional acute exposure mortality analyses of London data for the 1958 to 1959 through 1971 to 1972 winter periods, conducted by Mazumdar et al. (1982), Ostro (1984), Shumway et al. (1983), and by U.S. EPA (later published in Schwartz and Marcus, 1990). After assessing these various re-analyses and the previously

reviewed London results, the following conclusions were drawn (U.S. Environmental Protection Agency, 1986a,b):

(1) Markedly increased mortality occurred, mainly among the elderly and chronically ill, in association with BS and SO_2 concentrations above 1,000 $\mu g/m^3$, especially during episodes with such pollutant elevations over several consecutive days;

(2) During such episodes, coincident high humidity or fog was also likely important, possibly by providing conditions leading to formation of H_2SO_4 or other acidic aerosols;

(3) Increased risk of mortality is associated with exposure to BS and SO_2 levels in the range of 500 to 1,000 $\mu g/m^3$, for SO_2 most clearly at concentrations in excess of $\approx$700 $\mu g/m^3$; and

(4) Convincing evidence indicates that relatively small, but statistically significant, increases in mortality risk exist at BS (but not SO_2) levels below 500 $\mu g/m^3$, with no indications of any specific threshold level yet demonstrated at lower concentrations of BS (e.g., at $\leq$150 $\mu g/m^3$). However, precise quantitative specification of lower PM levels associated with mortality is not possible, nor can one rule out potential contributions of other possible confounding variables at these low PM levels.

The extensive epidemiological research that ensued has advanced our knowledge regarding the above issues, especially the roles played by PM and SO_2 in mortality and morbidity associated with non-episodic (lower level) exposures to these and/or other co-occurring pollutants. Key studies and findings from such research on mortality associated with short-term exposures to particulate matter are evaluated in the following subsection. Section 12.6.2 contains later additional discussion on the validity of model specifications.

12.3.1 Mortality Effects Associated with Short-Term Particulate Matter Exposures

The National Center for Health Statistics (NCHS) mortality statistics used in most U.S. mortality studies were compiled in accordance with World Health Organization (WHO) regulations, which specify that member nations classify causes of death by the current Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (World Health Organization, 1977). Causes of death for 1979 to 1991 were classified according to the ninth revision of the manual. For earlier years, causes of death were classified according to the revisions then in use—1968 through 1978, Eighth Revision; 1958 through 1967, Seventh

Revision; and 1949 through 1957, Sixth Revision. Changes in classification of causes of death due to these revisions may result in discontinuities in cause-of-death trends.

Mortality statistics are based on data coded by the States and provided to NCHS through the Vital Statistics Cooperative Program and from copies of the original death certificates received by the NCHS from the State Registration Offices. The National Center for Health Statistics (1993) reported that in 1991, in the United States, the death rate was 860.3 deaths per 100,000 population. In 1991 a total of 2,169,518 deaths occurred in the United States. The first three leading causes of death — diseases of the heart; malignant neoplasms; and cerebrovascular diseases — accounted for 64% of deaths. Chronic obstructive pulmonary disease and allied conditions surpassed accidents in 1991 as the fourth leading cause.

In 1991, life expectancy at birth reached a record high at 75.5 years. For those between 65 and 70 years of age, the average number of years of life remaining is 17.4 years. Women currently are expected to outlive men by an average of 6.9 years and white persons are expected to outlive black persons by an average 7.0 years. In 1991, the age-adjusted death rate for males of all races was 1.7 times that for females. In 1991, the age-adjusted death rate for the black population was 1.6 times that for the white population. The annual asthma death rate was consistently higher for blacks than for whites during the period 1980 through 1990; for blacks, the rate increased 52% (from 2.5 to 3.8 per 100,000), compared with a 45% increase (from 1.1 to 1.6 per 100,000) for whites (U.S. Centers for Disease Control, 1994). The National Center for Health Statistics (1994a) reported that, for January 1985 through December 1992, trends in mortality rates for diseases of the heart (including coronary heart disease) decreased. Mortality also showed a seasonal pattern, with death rates being higher in winter. Table 12-1 shows age specific and age-adjusted death rates for selected causes for 1979, 1990, 1991.

Samet et al. (1995) review deaths out of the hospital as a potentially sensitive indicator of a pollutant effect.

> "Clinical reports on case-fatality rates after patients are hospitalized for heart and lung disease support this emphasis on out-of-hospital deaths. Only a minority of persons hospitalized with heart and lung diseases die in the hospital, and life-support interventions probably alter the temporal relationship between an effect of pollution that leads to hospitalization and any eventual death. For example, in a recent U.S. study of community-acquired pneumonia (i.e., cases of pneumonia developing in persons living in the community), 16% of patients died in the hospital (Brancati et al., 1993). An even lower figure (4%) was reported from a study of community-acquired pneumonia in Sweden (Ortquist et al., 1990). Recent studies of myocardial infarction document a similar range

of survival rates during hospitalization (Jenkins et al., 1994; European Myocardial Infarction Project Group, 1993); even in patients with a prior myocardial infarction, mortality in the first 15 days following reinfarction was only 14% in a study in Israel (Moshkovitz et al., 1993). Surprisingly, only a minority of patients with COPD who are admitted with acute respiratory failure die while in the hospital, even though the condition of many patients is severe enough to warrant mechanical ventilation (Rieves et al., 1993; Weiss and Hudson, 1994). A pooled estimate from a recent series of patients hospitalized with COPD and acute respiratory failure showed an overall mortality rate of only 10% (Weiss and Hudson, 1994)."

12.3.1.1 Review of Short-Term Exposure Studies

The decade or so since the previous criteria document addendum was released (U.S. Environmental Protection Agency, 1986a) has been an active period for the reporting of time series analyses of associations between human mortality and acute exposures to PM (see Tables 12-2 and 12-3). In the beginning of this period, various PM measures of only

TABLE 12-1. AGE-SPECIFIC AND AGE-ADJUSTED UNITED STATES DEATH RATES FOR SELECTED CAUSES IN 1991 AND SELECTED COMPONENTS IN 1979, 1990, AND 1991 (Age-specific rates on an annual basis per 100,000 population in specified groups, age-adjusted per 100,000 U.S. standard million population)

Cause of death (Ninth Revision of International Classification of Diseases, 1975)	Year	Age								
		All ages[1]	Under 1 year[2]	1-4 years	45-54 years	55-64 years	65-74 years	75-84 years	85 years and over	Age-adjusted rate[3]
All causes	1991	860.3	916.6	47.4	468.8	1,181.0	2,618.5	5,890.0	15,107.6	513.7
	1990	863.8	971.9	46.8	473.4	1,196.9	2,648.6	6,007.2	15,327.4	520.2
	1979	852.2	1,332.9	64.2	589.7	1,338.0	2,929.0	6,496.6	14,962.4	577.0
Diseases of heart 390-398, 402, 404-429	1991	285.9	17.6	2.2	118.0	357.0	872.0	2,219.1	6,613.4	148.2
	1990	289.5	20.1	1.9	120.5	367.3	894.3	2,295.7	6,739.9	152.0
	1979	326.5	20.2	2.1	184.6	499.0	1,199.8	2,925.2	7,310.9	199.5
Hypertensive heart disease 402	1991	8.5	*	*	5.6	13.3	24.9	60.5	173.9	4.7
	1990	8.5	*	*	5.6	13.3	26.3	60.9	173.4	4.8
	1979	9.3	*	*	7.0	16.2	35.7	79.6	170.3	6.0
Ischemic heart disease 410-414	1991	192.5	0.5	*	75.5	240.5	605.8	1,536.7	4,374.1	99.1
	1990	196.7	0.7	*	77.7	248.6	627.0	1,602.5	4,498.1	102.6
	1979	245.5	0.7	*	136.1	381.0	926.6	2,224.8	5,376.1	149.7
Acute myocardial infarction 410	1991	93.3	*	*	45.0	138.2	326.3	752.9	1,669.4	51.5
	1990	96.1	*	*	46.5	144.3	342.1	793.6	1,695.5	53.7
	1979	133.8	*	*	94.6	258.9	577.2	1,135.2	1,916.3	88.2
Old myocardial infarction and other forms of chronic ischemic heart disease 412, 414	1991	97.5	*	*	29.2	99.4	273.9	772.2	2,671.5	46.6
	1990	98.8	*	*	29.7	101.3	279.0	796.7	2,769.4	47.8
	1979	109.4	*	*	39.3	117.0	340.3	1,072.2	3,424.9	59.9
Cerebrovascular diseases 430-438	1991	56.9	4.0	0.4	18.3	46.4	139.6	479.4	1,587.7	26.8
	1990	57.9	3.8	0.3	18.7	48.0	144.4	499.3	1,633.9	27.7
	1979	75.5	4.6	0.3	26.4	68.1	226.9	793.8	2,264.9	41.6
Chronic obstructive pulmonary diseases and allied conditions 490-496	1991	35.9	1.5	0.3	9.1	49.7	156.3	327.0	446.9	20.1
	1990	34.9	1.4	0.4	9.1	48.9	152.5	321.1	433.3	19.7
	1979	22.2	1.9	0.5	9.3	40.2	117.0	200.6	230.2	14.6
Pneumonia and influenza 480-487	1991	30.9	15.1	1.4	6.8	17.8	55.9	238.5	1,080.5	13.4
	1990	32.0	16.1	1.2	7.0	18.6	59.1	253.5	1,140.0	14.0
	1979	20.1	33.0	2.0	7.1	16.4	47.8	184.2	694.9	11.2

[1]Figures for age not stated are included in "All ages" but not distributed among age groups.
[2]Death rates under 1 year (based on population estimates) differ from infant mortality rates (based on live births).
[3]For method of computation, see technical notes in Source.

Source: National Center for Health Statistics (1993a).

*See technical notes in reference source.

TABLE 12-2. SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
KM (mean = 25; SD = 11)	Total, respiratory, and cardiovascular mortality in Los Angeles County (1970 to 1979) related to O_3, CO, SO_2, NO_2, HC, daily max. temp., RH, and KM (a PM metric of optical reflectance by particles, related to ambient carbon and fine particle concentration). Low pass filter used to eliminate short-wave, so that only long- wave associations studied.	Frequency domain analyses indicated stat. signif. ($p<0.05$) short- and long-wave associations with KM. The filtered (i.e., long-wave) data analysis also indicated that air pollution (including KM) was significantly associated with seasonal variations in LA mortality.	Shumway et al. (1988)
KM (mean = 25; SD = 11)	Los Angeles mortality (1970 to 1979) dataset of Shumway et al. (1988) analyzed using a high-pass filter to allow investigation of short-wave (acute) associations with environmental variables (by removing seasonality effects). Environmental variables considered in regression analyses included temp., RH, extinction coefficient, carbonaceous PM (KM), SO_2, NO_2, CO, and O_3.	Analyses showed stat. significant associations between short-term variations in total mortality and pollution, after controlling for temperature. Day-of-week effects did not to affect the relationships. Results demonstrated significant mortality associations with O_3 lagged 1 day, and with temp., NO_2, CO, and KM. Latter three pollutants highly correlated with each other, making it impossible to separately estimate PM associations with mortality.	Kinney and Ozkaynak (1991)
COH (monthly mean range = 9 to 12)	Daily total, respiratory, cancer, and circulatory mortality associations with daily COH in Santa Clara County, CA (1980 to 1982 and 1984 to 1986 winters). Daily mean temp. and RH at 4 p.m. also considered.	An association found between COH and increased mortality, even after adjustments for temperature, relative humidity, year, and seasonality.	Fairley (1990)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
BS (mean = 90.1 μg/m^3) (24-h avg. daily max. = 709 μg/m^3)	Daily total mortality analyzed for associations with BS, SO_2, and H_2SO_4 in London, England, during 1963 to 1972 winters. Mean daily temp. and RH also considered.	PM, SO_2, and H_2SO_4 all found to have stat. signif. associations with mortality (0, 1 day lag). Temp. also correlated (negatively) with mortality, but with 2-day lag. Seasonality addressed by studying only winters and by applying high-pass filter to the series and analyzing residuals.	Thurston et al. (1989)
BS (mean = 90.1 μg/m^3) (range = 0 to 350 μg/m^3)	Further analysis of London, England data (1965 to 1972) examined by Thurston et al. (1989). Spectral and advanced time series methods used, e.g. prewhitening and auto- regressive (AR) moving average (MA) methods. Variables considered included BS, SO_2, H_2SO_4, temp., and RH.	Estimated pollution mean effect of 2 to 7% of all London winter deaths (mean = 281/day), but various pollutants' effects not separated. Independent model test on 1962 episode confirmed appropriateness of such methods. Long-wave addressed by considering winters only and by prewhitening the data.	Ito et al. (1993)
Suspended Particles (SP) (range = 10 to 650 μg/m^3)	Daily total mortality in Erfurt, East Germany, during 1980 to 1989 (median = 6/day) related to SO_2, SP, T, RH, and precipitation. SP only measured 1988 to 1989. Autoregresssive Poisson models used (due to low deaths/day) also included indicator variables for extreme temp. and adjustments for trend, season, and influenza epidemics.	Both SO_2 and SP found to be significantly associated with increased mortality. In a simultaneous regression, SP remained significant while SO_2 did not. Correlations of these coefficients not provided, however. Pollution effect size similar to that for meteorology.	Spix et al. (1993)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
BS	Daily total mortality in Athens, Greece, and surrounding boroughs (1975 to 1987) related to BS, SO_2, NO_2, O_3, and CO_2 using multiple regression.	During winter months 1983 to 1987, the daily number of deaths was positively and statistically significantly associated with all pollutants, but the association was strongest with BS.	Katsouyanni et al. (1990a)
BS (annual mean range = 51.6 to 73.3 µg/m^3) (maximum daily value = 790 µg/m^3)	For 1975 to 1982 in Athens, Greece 199 days with high SO_2 (>150 µg/m^3) each matched on temp., year, season, day of week, and holidays with two low SO_2 days. Mortality by-cause compared between groups by ANOVA by randomized blocks. BS correlated with SO_2 at r = 0.73, but not directly used in analysis.	Mortality was generally higher on high SO_2 days, with the difference being most pronounced for respiratory conditions. BS levels for each group not provided, and BS-SO_2 confounding not addressed, limiting interpretability of results.	Katsouyanni et al. (1990b)
BS (range = 50 to 250 µg/m^3)	Daily total mortality in Athens, Greece, during July, 1987 (when a major heat wave occurred) compared to deaths in July for previous 6 yr. Variables considered included: BS, SO_2, temp., discomfort index (DI). Effects of day-of-week, month, and long-term trends addressed via dummy variables in OLS regression models.	Mean daily temperature above 30 °C found to be significantly associated with mortality. The main effects of all air pollutants nonsignificant, but the interaction between high air pollution and temp. significant for SO_2 and suggestive ($p < 0.20$) for ozone and BS.	Katsouyanni et al. (1993)
BS (mean = 83 μg/m^3) (range = 18 to 358 μg/m^3)	Daily total mortality in Athens, Greece, during 1984-1988 (mean = 38/day) related to BS, SO_2, CO, T, and RH. Autoregressive OLS models employed also included indicator variables for season, day of week, and year.	BS, SO_2, and CO each individually significantly associated with increased mortality. The size of all coefficients declined in simultaneous regressions, with SO_2 still significant and BS approaching significance. CO was no longer significant, but highly correlated with BS (r = 0.74).	Touloumi et al. (1994)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 87 µg/m^3) (24-h avg. range: 46 to 137 µg/m^3, 5th to 95th percentiles)	Total deaths in Detroit, MI (1973 to 1982) analyzed using Poisson methods. Variables considered included TSP, SO_2, O_3, temp., and dew point. Seasonality controlled via multiple dummy weather and time variables.	Signif. associations between mortality and TSP in autoregressive Poisson models (RR for 100 µg/m^3 TSP = 1.06). Most TSP data estimated from visibility, which is best correlated with fine particle portion of TSP. Thus, results suggest a fine particle association.	Schwartz (1991a)
TSP (mean = 77 μg/m^3) (max. = 380 μg/m^3) (5th to 95th percentiles = 37 to 132 μg/m^3)	Total and cause-specific daily mortality in Philadelphia, PA (1973 to 1980) related to daily TSP and SO_2 (n $\approx$2,700 days). No other pollutants considered in analysis. Poisson regression models, using GEE methods, included controls for year, season, temp., and RH. Autocorrelation addressed via autoregressive terms in model.	Strongest mortality associations with pollution on same and prior days. Total mortality (mean = 48/day) estimated to increase 7% (95% C.I. = 4 to 10%) for a 100 μg/m^3 increase in TSP. Larger cause-specific effects of TSP (as %). SO_2 associations non-significant in simultaneous models with TSP, but correlations of estimated coefficients not reported.	Schwartz and Dockery (1992a)
TSP (mean 65 range 14 to 338)	Reanalyses of Philadelphia mortality data, 1973-1988. Poisson regression models by season, adjusted for weather, year, SO_2, and O_3.	Relationship between TSP and mortality appears to be sensitive to inclusion of SO_2 or O_3, and differs by season.	Moolgavkar et al. (1995b)
TSP	Reanalyses of Philadelphia mortality data, 1973-1990, using filtered autoregressive regression models. Adjustments for weather, SO_2, O_3, and season, with particular attention to subset analyses for weather. Sensitivity analyses for lag structure.	TSP associated with mortality on hottest days, suggesting possible interaction. Little relationship of O_3 to mortality except on coldest days. Correlation structure suggests short-term mortality displacement.	Wyzga and Lipfert (1995b)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 69 $\mu g/m^3$) (5th to 95th percentiles = 32 to 120 $\mu g/m^3$)	Age and cause-specific daily mortality in Philadelphia, PA during 1973 and 1990 related to daily TSP, SO_2, and O_3. Other variables included were: temp., RH, barometric pressure, precipitation. Various models used, including poisson and autoregessive. Also applied prefiltering methods to remove long-waves.	TSP effect found only in winter. TSP never significant in by-cause analyses of those <15 or ≥65 years old. Addition of other pollutants (TSP-SO_2 r = 0.57) weakened TSP effects. Including barometric pressure and precipitation in the models may have acted as surrogates for PM, potentially confounding results. TSP correlations with other variables not given.	Li and Roth (1995)
TSP, Philadelphia (mean = 77.2, range = 22 to 338)	Reanalyses of 1973-1980 mortality in Philadelphia from Dockery and Schwartz (1992a), Moolgavkar et al. (1995a). Sensitivity analyses done for TSP and SO_2 relation to total mortality and for elderly and non-elderly mortality, including adjustments for season, weather, time trend, lags, and moving averages. Analyses also for total cardiovascular mortality, pneumonia and emphysema mortality, cancer mortality. Poisson regression and various autoregressive models compared. Nonparametric LOESS models for mortality vs. TSP and SO_2 developed. Quantile models assessed for TSP, SO_2, weather.	Control for weather variables had little effect on results. Both TSP and SO_2 had effects on mortality, but TSP had little effect unless TSP > 100 $\mu g/m^3$, whereas SO_2 had a positive effect on mortality at lower concentrations, but showed little relation at higher concentrations. Seasonal effects important, with TSP dominant in summer and SO_2 in winter. Lag structures analyses confirmed earlier findings of greater effect from more recent exposures.	Samet et al. (1995)
TSP	Reanalyses of 1973-1980 Philadelphia mortality data with emphasis on model specification for weather variables. Additive Poisson regression models fitted to TSP and SO_2, adjusting for time trend and weather. The weather adjustments tested were of original investigators (Schwartz and Dockery, 1992a) and two different synoptic weather categories. Both nonparametric regressions and LOESS used.	The associations of mortality to TSP and SO_2, alone or together not attributable to differences in the weather model. Models that can be adjusted to fit the mortality data provides a better fit than objective weather models not adjusted to mortality. Little evidence that weather categories modified the TSP effect.	Samet et al. (1996b)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 37 $\mu g/m^3$) range = 14 to 222	Reanalyses of 1974-1988 Philadelphia mortality data with emphasis on copollutants. Additive linear Poisson regression models fitted with TSP, SO_2, NO_2, and O_3, over same plus preceding day, as well as lagged CO(LCO) averaged over 3- and 4-day lags. All pairs of pollutants tested as well as models with 5 or 6 pollutants. Models adjusted for weather, time, season, and day of week.	O_3 and LCO has significant positive effects on mortality not confounded with other pollutants. TSP and SO_2 not sig. when both in models, but had larger and more sig. effects when other pollutants included. Seasonality important, with TSP larger effect in spring and summer and O_3 in fall and winter. NO_2 had no sig. effect unless TSP and SO_2 in model. CO never had significant effect.	Samet et al. (1996a)
TSP	Reanalyses of 1983-1988 total mortality data for Philadelphia, by sex, race, age, and place of death. Poisson regression models adjusted for weather and time were fitted to additive linear models including SO_2 and O_3. Sensitivity to TSP model specification was tested using liner and piecewise linear models and quintile models for TSP. Lagtime and moving average models were compared. Mortality displacement was assessed by comparing mortality residuals and episodes.	A positive and significant TSP effect found, while O_3 was marginally significant and SO_2 not significant. The TSP effect was similar when data divided by sex, race, age group, and place of death. There appeared to be a smaller TSP effect at concentrations below about 60 to 90 $\mu g/m^3$ than at concentrations above 100 $\mu g/m^3$. A substantial number of the excess deaths during TSP episodes appeared to be a few days premature.	Cifuentes and Lave (1996)
TSP (mean = 111 $\mu g/m^3$) (24-h avg. range: 36 to 209 $\mu g/m^3$, 10th to 90th percentiles)	Daily total mortality in Steubenville, OH (1974 to 1984) related to TSP, SO_2, temp., and dew point. Poisson regression used, because of very low death counts/day (mean = 3.1). Regressions controlled for season by including dummy variables for winter and spring, and autoregressive methods used to address any remaining autocorrelation.	In regressions controlling for season and weather, previous day's TSP was significant predictor of daily mortality. SO_2 was less significant in regressions, becoming nonsignificant when entered simultaneous with TSP. Auto-regressive models gave similar results.	Schwartz and Dockery (1992b)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure x(Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 113 $\mu g/m^3$) (10th to 90th percentiles = 38 to 212 $\mu g/m^3$)	Daily mortality in Steubenville, OH (1974 to 1984) related to TSP, SO_2, temp., and dew point (to allow comparisons of results with Schwartz and Dockery, 1992b). Poisson method used; analyses done overall and by-season at same time period and location as in Schwartz and Dockery (1992b).	In single pollutant models, TSP coefficient was same as in Schwartz and Dockery (1992b), but TSP effects attenuated by SO_2 inclusion in the model. SO_2 also attenuated by addition of TSP. Concluded that TSP and SO_2 effects cannot be separated in this dataset. Intercorrelations among these variables not presented.	Moolgavkar et al. (1995a)
TSP (mean = 52 µg/m^3; SD = 19.6 µg/m^3)	Daily total and cause-specific mortality in Cinci., OH (mean total = 21/day) during 1977 to 1982 related to TSP, temp., dew point. Poisson model used with dummy variables for each month and for eight (unspecified) categories of temp. and dew point. Linear and quadratic time trend terms also included, spline and nonparametric models applied. Autocorrelation not directly addressed.	TSP significantly associated with increased risk of total mortality. Relative risk higher for elderly and for those dying of pneumonia and cardiovascular disease. However, the analysis did not consider other pollutants, and there remains the potential for within-month, long-wave confoundings.	Schwartz (1994a)
TSP (OECD Method) (Lyons, France: 3 year mean = 87 µg/m^3) (Marseilles, France 3 y mean = 126 µg/m^3)	Daily total, respiratory, and cardiac mortality for persons $\geq$65 years of age tested for associations with SO_2 and TSP during 1974 to 1976 in Lyons and Marseilles, France. Temperature also considered in analyses.	No sig. mortality associations found with TSP, but SO_2 reported as associated with total elderly deaths in both cities. Seasonality addressed by analyzing deviations from 3-year average of 31-day running means of variables, but temp. lags not considered and probable seasonal differences in winter/summer temp.-mortality relationship not addressed.	Derriennic et al. (1989)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 375 µg/m^3) (maximum = 1,003 µg/m^3)	Daily deaths during 1989 in two residential areas in Beijing, China (mean total deaths = 21.6/day) related to TSP and SO_2 using Poisson methods. Controlling for other variables included quintiles of temp. and humidity. Long-wave confounding and autocorrelation not directly addressed, but season-specific results presented.	Sig. mortality associations for ln (SO_2) and ln (TSP). Associations strongest for chronic respiratory diseases. In simultaneous regressions, SO_2 sig., but not TSP. However, the two pollutants highly correlated with each other (r = 0.6), as well as with temp.; in season-specific analyses, both were sig. in summer, but only SO_2 in winter.	Xu et al. (1994)
PM_{10} (mean = 47 µg/m^3) (24 h max. = 365 µg/m^3) (5 day max. = 297 µg/m^3)	Total, respiratory, and cardiovascular mortality in Utah County, UT (1985 to 1989) related to 5-day moving average PM_{10}, temp., and RH. Time trend and random year terms also included in autoregressive Poisson models. Seasonality not directly addressed in basic model, but addition of four seasonal dummy variables changed results little.	Significant positive association between total non-accidental mortality. Strongest association with the 5-day moving average of PM_{10}. Association largest for respiratory disease, next largest for cardiovascular, and lowest for all other. Association seen below 150 µg/m^3 PM_{10}. Possible influences of other pollutants discussed, but not directly addressed.	Pope et al. (1992)
PM_{10} (mean = 47 µg/m^3) (range = 1-365 μg/m^3)	Reanalyses of Utah Valley mortality date for 1985-1989 with emphasis on alternative model specifications for weather. Poisson regression models fitted to all cause, pulmonary, and cardiovascular mortality, using moving averages of PM_{10} up to 5 days after adjustment for time trend and weather. Sensitivity to weather adjustments tested by comparing LOESS models, 19 synoptic weather categories, and quintile indicators. Models with hot/cold season also tested. Both linear and LOESS models for PM_{10} used.	The estimated PM_{10}-mortality relationship remained positive, significant, and only moderately sensitive to any of the alternative model specifications for weather. The relative risk was somewhat larger for cardiovascular mortality, but much higher for pulmonary mortality. Longer PM_{10} averaging times (4-6 days) provided best fit to mortality from all causes.	Pope and Kalkstein (1996)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} St. Louis, MO: (mean = 28 μg/m^3) (24 h max. = 97 μg/m^3) Kingston/Harriman, TN (mean = 30 μg/m^3) (24 h max. = 67 μg/m^3)	Total mortality in St. Louis, MO and Kingston/Harriman, TN plus surrounding counties (September 1985 to August 1986) related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temp., dew point, and season using auto-regressive Poisson models.	In St. Louis, statistically significant daily mortality associations with PM_{10} and $PM_{2.5}$, but not other pollutants. In Kingston/Harriman, PM_{10} and $PM_{2.5}$ approached significance, but not other pollutants. Seasonality reduced by season indicator variables, but within season long wave cycles not directly addressed.	Dockery et al. (1992)
PM_{10} (mean = 48 μg/m^3) (24 h max. = 163 μg/m^3)	Total daily mortality in Birmingham, AL (from August 1985 to December 1988) related to PM_{10}, temp, dew point. Poisson models used addressed seasonal long wave effects by including 24 sine and cosine terms having periods of 1 mo to 2 years. Autoregressive linear models also applied.	Significant associations between total mortality and prior day's PM_{10}. Various models gave similar results, as did eliminating all days with PM_{10} >150 μg/m^3. However, possible roles of other pollutants not evaluated.	Schwartz (1993a)
PM_{10} (mean = 40 μg/m^3) (24 h max. = 96 μg/m^3)	Total, cardiovascular, cancer, and respiratory mortality in Toronto, Canada (during 1972 to 1990) related to PM_{10}, TSP, SO_4, CO, O_3, temp., and RH. Moving average (19-day) filtered data used in OLS regressions. Using model developed from 200 PM_{10} sampling days during the period, 6303 PM_{10} values estimated based on TSP, SO_4, COH, visibility (B_{ext}) and temp. data.	Significant associations between mortality and all pollutants considered, after controlling for weather and long wave influences. However, not possible to separate PM_{10} association from other PM measures. Simultaneous PM and ozone regressions gave significant coefficients for each, but intercorrelations among pollutants not presented.	Ozkaynak et al. (1994)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (mean = 58 μg/m^3) (24 h max. = 177 μg/m^3)	Total mortality in Los Angeles, CA (during 1985 to 1990) related to PM_{10}, O_3, CO, temp., and RH. Poisson models used addressed seasonal long-wave influences by including multiple sine and cosine terms of 1 mo to 2 years in periodicity. OLS and log linear models also tested. Winter and summer also analyzed separately.	PM_{10} and mortality associations only mildly sensitive to modeling method. CO also individually significant. Addition of either CO or O_3 lowered significance of PM_{10} in model somewhat, but PM_{10} coefficient not as affected, indicating minimal effects on PM_{10} association by other pollutants in this case.	Kinney et al. (1995)
PM_{10} (mean = 38 μg/m^3) (24 h max. = 128 μg/m^3)	Total mortality in Los Angeles, CA and Chicago, IL during 1985 through 1990 related to PM_{10}, O_3, and temperature. Analysis focused on importance of monitor choice to modeling results. Poisson models used addressed seasonal long wave influences by including multiple sine/cosine terms ranging from 1 mo to 2 years in periodicity.	Average of multiple sites' PM_{10} significantly associated with mortality in each city after controlling for season, temperature and ozone. Other pollutants and relative humidity not yet considered. Individual sites' PM_{10} varied from non-significant to strongly significant. Also, dividing the data by season diminished the significance of the multi-site average PM_{10} in mortality regressions. Both site selection and sample size concluded to influence results.	Ito et al. (1995)
PM_{10} (mean = 115 μg/m^3) (24 h max. 367 μg/m_3)	Total, respiratory, and cardiovascular daily deaths/day (means = 55, 8, and 18, respectively) in Santiago, Chile during 1989 through 1991 related to PM_{10}, O_3, SO_2, NO_2, temperature and humidity. Seasonal influences addressed by various methods, including seasonal stratification, the inclusion of sine/cosine terms for 2.4, 3, 4, 6, and 12 month periodicities, prefiltering, and the use of a nonparametric fit of temperature. Log of PM_{10} modeled using OLS with first order autoregressive terms.	Significant association found between PM_{10} and daily mortality, even after addressing potential confounders (e.g., weather), other pollutants, lag structure, and outliers. Strongest associations found for respiratory deaths. SO_2 and NO_2 each also significantly associated, but only PM_{10} remained significant when all added simultaneously to the regression. Correlations of the coefficients not reported.	Ostro et al. (1996)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (mean = 82.4 $\mu g/m^3$) (24 h avg. SE = 38.9 $\mu g/m^3$)	Respiratory mortality among children < 5 years old (mean = 3/day) in Sao Paulo, Brazil during May 1990 through April 1991 related to PM_{10}, SO_2, NO_x, O_3, CO, temperature, humidity, and day of week. Season addressed by including seasonal and monthly dummy variables in regressions. Mortality data adjusted for non-normality via a square root transformation.	Significant association found between respiratory deaths and NO_x, but no other pollutants. No such association found for non-respiratory deaths. However, auto-correlation not addressed. Also, inter-correlations of the pollutant coefficients not reported (but NO_x - PM_{10} correlation = 0.68)	Saldiva et al. (1994)
PM_{10} (mean = 82.4 $\mu g/m^3$) (24 h avg. SE = 38.9 $\mu g/m^3$)	Total mortality among the elderly ($\geq$ 65 years old) (mean = 63/day) in Sao Paulo, Brazil during May 1990 through April 1991 related to two day avg. of PM_{10}, SO_2, NO_x, O_3, and CO, and to temperature, humidity, and day of week. Season addressed by including seasonal and monthly dummy variables. Temperature addressed using three discrete dummy variables.	Significant associations found between total elderly deaths and all pollutants considered. In a simultaneous regression, PM_{10} was the only pollutant which remained significant. The PM_{10} coefficient actually increased in this regression, suggesting interpollutant interactions. Correlations of the pollutant coefficients not provided.	Saldiva et al. (1995)
PM_{10} (Cook County median = 37 $\mu g/m^3$; max = 365 $\mu g/m^3$) (Salt Lake County median = 35 $\mu g/m^3$; max = 487 $\mu g/m^3$)	Total, respiratory, circulatory, and cancer mortality in Cook County (1985 to 1990). Elderly, total by race and sex also evaluated. Poisson regression with seasonal adjustments, meteorological variables, and pollen tested. In Salt Lake County, total and elderly mortality. One daily station in Cook County and two daily monitoring stations in Salt Lake County, plus multiple every 6th-day stations.	Average and single site PM_{10} were significant predictors in Cook County for total, elderly, cancer, and elderly white mortality, marginal for respiratory, circulatory, and elderly black. Significant Fall and Spring mortality in Cook County, not Summer or Winter. No significant effects in Salt Lake County. No copollutants.	Styer et al. (1995)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (variable by month and year)	Reanalysis of Utah County mortality (1985 to 1992), broken down by year, season, cause and place of death. PM_{10} entered as dichotomous variable (less or greater than 50 $\mu g/m^3$). No adjustment for copollutants or weather in Poisson regression, except for daily minimum temp. Poisson regression, not GEE.	Variations in RR did not appear to be associated with high or low PM_{10} days. High RR for cancer deaths (age < 60) at home. Highest RR in spring. Also, increased RR for sudden infant death syndrome.	Lyon et al. (1995)
PM_{10} (mean 41 ± 19 $\mu g/m^3$)	Total deaths, circulatory, cancer, respiratory, and other deaths in Cook County, IL for 1985-90 were related to PM_{10} other pollutants using Poisson regression models adjusted for weather season, time trend, and day of week. Analyses were carried out for race and gender.	Significant positive associations were found between PM_{10} and total mortality similar to other studies. Higher sig. effects were found for respiratory and for cancer mortality, while circulatory deaths showed a small positive non-sig. association. Other causes showed no relationship. African-American females showed a significantly higher risk for total mortality.	Ito and Thurston, (1996)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10}: Portage, WI 18 ± 12 $\mu g/m^3$ Boston, MA 24 ± 13 $\mu g/m^3$ Topeka, KS 27 ± 16 $\mu g/m^3$ St. Louis, MO 31 ± 16 $\mu g/m^3$ Knoxville, TN 32 ± 15 $\mu g/m^3$ Steubenville, OH 46 ± 32 $\mu g/m^3$ $PM_{2.5}$: Portage, WI 11 ± 8 $\mu g/m^3$ Boston, MA 16 ± 9 $\mu g/m^3$ Topeka, KS 12 ± 7 $\mu g/m^3$ St. Louis, MO 19 ± 10 $\mu g/m^3$ Knoxville, TN 21 ± 10 $\mu g/m^3$ Steubenville, OH 30 ± 22 $\mu g/m^3$	Total COPD, IHD, pneumonia, and elderly mortality in six cities from 1979 to 1988 related separately to every-other-day. $PM_{10/15}$, $PM_{2.5}$, CP = $PM_{(15-2.5)}$, $SO_4^=$, and H^+, after adjustment for temp., dewpoint, time trend, indicators for rain, snow, day of week. Combined analyses for both $PM_{2.5}$ and CP. Poisson regressions linear in PM index, with nonparametric fits for weather and time. Lag structure not investigated. Variance-weighted combined estimates. Sensitivity analyses for weather control, nonlinear effect of $PM_{2.5}$.	Significant positive relationships for total mortality vs $PM_{2.5}$ in three cities, positive but less significant in others. Significant positive relationships for total mortality vs PM_{10} in four cities, positive but weather in Portage, negative but not sig. in Topeka. No significant relationship between CP and mortality except in Steubenville. Combined analyses sig. and positive for all causes, with larger effects in elderly and for IHD, COPD, and pneumonia. Smaller sig. relationship of mortality to $SO_4^=$, relationship to H^+ was small non-sig. No analyses of copollutants.	Schwartz et al., (1996a)

TABLE 12-3. INTERCOMPARISONS OF PUBLISHED PARTICULATE MATTER-ACUTE MORTALITY STUDY RESULTS BASED ON CONVERSION OF VARIOUS PARTICULATE MATTER MEASURES TO EQUIVALENT PM_{10} ESTIMATES

Health Outcome	Synthesis Study	Location	Original PM Measurement	Mean Equivalent PM_{10}	Percent Change Per 10 $\mu g/m^3$ PM_{10} Equivalent	95 Percent Confidence Interval
Total Mortality	Ostro (1993)	London UK	BS	80	0.3	(0.29, 0.31)
		Steubenville OH	TSP	61	0.6	(0.44, 0.84)
		Philadelphia PA	TSP	42	1.2	(0.96, 1.44)
		Santa Clara CA	COH	37	1.1	(0.73, 1.51)
	Dockery and Pope (1994b)	St. Louis MO	PM_{10}	28	1.5	(0.1, 2.9)
		Kingston TN	PM_{10}	30	1.6	(-1.3, 4.6)
		Birmingham AL	PM_{10} (3d)[1]	48	1.0	(0.2, 1.5)
		Utah Valley UT	PM_{10} (5d)[2]	47	1.5	(0.9, 2.1)
		Philadelphia PA	TSP (2d)[3]	40	1.2	(0.7, 1.7)
		Detroit MI	TSP	48	1.0	(0.5, 1.6)
		Steubenville OH	TSP	61	0.7	(0.4, 1.0)
		Santa Clara CA	COH	35	0.8	(0.2, 1.5)
Respiratory Mortality	Dockery and Pope (1994b)	Birmingham AL	PM_{10} (3d)	48	1.5	(-5.8, 9.4)
		Utah Valley UT	PM_{10} (5d)	47	3.7	(0.7, 6.7)
		Philadelphia PA	TSP (2d)	40	3.3	(0.1, 6.6)
		Santa Clara CA	COH	35	3.5	(1.5, 5.6)
Cardiovascular Mortality	Dockery and Pope (1994b)	Birmingham AL	PM_{10} (3d)	48	1.6	(-1.5, 3.7)
		Utah Valley UT	PM_{10} (5d)	47	1.8	(0.4, 3.3)
		Philadelphia PA	TSP (2d)	40	1.7	(1.0, 2.4)
		Santa Clara CA	COH	35	0.8	(0.1, 1.6)

[1]Three day moving average.
[2]Five day moving average.
[3]Two day moving average.

indirect applicability to the standard setting process (e.g., TSP, BS, KM, or COH) were usually employed. However, in the last few years the analyses have more often employed PM_{10} as a measure of PM. This is because sufficient routine PM_{10} ambient measurement data began to be available for such statistical analyses to be conducted in a wide variety of locales. The focus of this section is on detailed assessments of those studies conducted since the PM criteria document addendum (U.S. Environmental Protection Agency, 1986a). Of special interest are studies that have employed PM_{10} in their analyses of the human mortality effects of acute exposures to PM; although studies employing other indices of PM exposures are summarized in tables and discussed in the text, as appropriate.

As shown in Table 12-2, a variety of PM metrics have been employed in time-series studies relating PM to acute mortality. These have included gravimetric measures, such as total suspended particulate matter (TSP) and PM_{10}, the former of which measures a significant portion of extrathoracic particles. In addition, many studies have employed data from various samplers that yield BS or KM optical measurements of particle reflectance of light, or coefficient of haze (COH) optical measurements of particle transmission of light. All of these latter metrics (BS, KM, COH) are most directly related to ambient elemental carbon concentration (e.g., see Bailey and Clayton, 1982; Wolff et al., 1983; Cass et al., 1984), but only indirectly related to particle (most closely fine particle) mass, as the relationship with mass will vary as sampled particle size, shape, color, and surface characteristics vary over time and between sites. Hence, unless side-by-side calibrations of these optical measurements are made against direct mass measurements obtained by collocated gravimetric monitoring instruments, such optical measurements cannot be readily converted to quantitative estimates of ambient PM mass concentrations or associated PM-mortality relationships. Thus, given the diversity of nonequivalent PM metrics employed across many of the reviewed epidemiology studies, attempting quantitative intercomparisons between results of all of the various reviewed epidemiologic studies necessarily introduces additional uncertainties, although attempts have been made by using conversion factors (Schwartz, 1992a; Ostro, 1993; Dockery and Pope, 1994b; Lipfert and Wyzga, 1995a; Pope et al., 1995a). Lipfert and Wyzga (1995a,b) report results in terms of elasticities, which do not require conversion factors.

The two studies using KM as the PM metric employed very different approaches to the same data set from Los Angeles during 1970 to 1979. The study by Shumway et al. (1988)

evaluated long-wave associations and found significant KM-mortality associations, but this analysis did not assess for seasonal effects. The KM study by Kinney and Ozkaynak (1991) more appropriately studied the short-wave associations of multiple pollutants, finding KM to be significantly associated with total mortality, but collinearities among KM, NO_2, and CO made it "impossible to uniquely estimate their separate relationships to mortality."

Similar to the KM studies, BS studies are quite varied in approach. Thurston et al. (1989) applied a high pass filter (similar to that employed by Kinney and Ozkaynak, 1991) to the 1963 to 1972 London, England wintertime mortality-pollution data set, whereas Ito et al. (1993) analyzed a subset of the same data using prewhitening and autoregressive techniques. In both, BS, SO_2, and H_2SO_4 were all found to be significantly associated with mortality, but the effects of each were not separable due to the high collinearity among these pollution metrics. Katsouyanni et al. (1990a) similarly found an association between total mortality and all pollutants measured in Athens, Greece during 1975 to 1987, although they reported BS to be most strongly associated. A separate randomized block analysis of SO_2 and by-cause mortality during this same period (Katsouyanni et al., 1990b) found significant SO_2 effects, but SO_2 and BS were correlated at $r = 0.73$. A subsequent analysis by Katsouyanni et al. (1993) of summer heat wave periods found a significant temperature-SO_2 interaction term, and the suggestion of an interaction ($p < 0.2$) for BS.

A study using BS as the PM index which carefully addressed potential confounding effects of other pollutants and temperature was conducted by Touloumi et al. (1994) for daily all-cause mortality in Athens, Greece during 1984 through 1988. In this study, BS (mean = 83 $\mu g/m^3$), SO_2 (mean = 45 $\mu g/m^3$), CO (mean = 6 $\mu g/m^3$), temperature, and relative humidity were all modeled separately and simultaneously, giving a range of estimates for PM effects, depending on the model specification. The five years of data employed provided ample numbers of records for the analysis (e.g., $n = 1684$ for BS). Temperature associations were simply but effectively modeled. The authors examined the bivariate temperature-mortality plot and noted a mortality minimum around 23 °C daily mean temperature. They then defined two temperature variables: one as the daily mean temperature deviation below 23 °C; the other as the daily deviation above 23 °C (whichever was relevant), thereby allowing a separate modeling of the cold and hot weather effects on mortality. The square of each of these (lagged one day) gave the best fit of the mortality, and these terms were used in subsequent pollutant models. Multiple

monitoring stations were averaged (e.g., 5 for BS) after filling in missing observations from available data on the same day at other sites, providing spatially representative exposure estimates. Ordinary least squares modeling was applied, which is acceptable in this case given the relatively large number of mortality counts/day (mean = 38 deaths/day, SE = 12) in this metropolitan area. Day-of-week, season, hot (> 23 °C) and cold (<23 °C) temperature deviations squared, and relative humidity terms were also included in mortality regressions on pollutants. Although the use of only a dummy term for each season could not have fully addressed the within-season long wave mortality trends shown in time series plots, autoregressive modeling did address any resulting residual autocorrelation. Also, use of a single annual sine curve with periodicity of 1 year (phase not reported) gave similar results.

Separating the effects of the various air pollutants was attempted in this analysis of Athens mortality, but proved challenging. The log of pollutant concentrations were entered into the basic model both individually and simultaneously. All pollutants considered were individually significant at the $p = 0.0001$ level. When copollutants were simultaneously entered, SO_2 was the least affected, both in terms of coefficient size and statistical significance. The BS coefficient dropped in size by 50% when entered with SO_2 in the model, and its statistical significance weakened (as expected when correlated variables are entered together) but remained significant ($p = 0.02$, two-tailed test). However, SO_2 declined by less than 30 percent and remained significant at the $p = 0.002$ level in simultaneous regressions. The CO coefficient decreased in size by 75% and became clearly non-significant when entered with either SO_2 or BS. The authors noted, however, that these pollutants are highly intercorrelated over time (e.g., for CO and BS, $r = 0.79$). Thus, while the most consistent mortality association, both in terms of size and significance of its coefficient, appears to be with SO_2 in this city, the colinearities among these primary, combustion-related, air pollutants precludes quantitative apportionment of effects to individual pollutants. The authors acknowledged this, concluding that relatively low-level air pollution has a small but real effect on mortality. Using BS alone as the index of ambient air pollution, the authors reported that a 10% decrease in BS to be associated with a 0.75% decrease in total mortality. Using an on-site calibration with PM_{10} ($PM_{10} = 8.70 + 0.832 \times BS$) developed for this city (Katsouyanni, 1995) yields a mean PM_{10} of 77.7 $\mu g/m^3$ and a relative risk (RR) of 1.07 for a 100 $\mu g/m^3$ increase in PM_{10} (i.e., to 203 $\mu g/m^3$ BS). However, when the BS coefficient from the simultaneous regression with other pollutants is used, the estimated RR per

100 $\mu g/m^3$ increase in PM_{10} drops to 1.03. Thus, the estimate of the total mortality RR of a one day 100 $\mu g/m^3$ increase in PM_{10} implied by this work ranges from 1.07 to 1.03, depending on whether the PM metric is entered into the regression singly or in combination with other pollutants, respectively.

Recent Studies Using TSP

Studies evaluating TSP effects have also yielded mixed results as to the relative role of PM, versus other pollutants, in mortality. For example, Schwartz (1991a) examined total mortality in Detroit during 1973 to 1982, finding TSP to be more strongly associated with mortality than SO_2. However, the correlation between SO_2 and TSP was not reported, other pollutants likely to have been present (e.g., CO and NO_2) were not considered in the analysis, and most of the TSP values were estimated from visibility records, which are most strongly correlated with fine particles (e.g., see Ozkaynak et al., 1986). The Schwartz and Dockery (1992b) analysis of 1974 to 1984 mortality in Steubenville, OH similarly concluded that TSP was more significant than SO_2, but neither considered other pollutants nor reported the correlation between SO_2 and TSP in this valley locale. A Schwartz (1994a) analysis of Cincinnati, OH, mortality during 1977 to 1982 also found a TSP-mortality association, but did not consider other pollutants. Derriennic et al. (1989) examined mortality among the elderly in two French cities during 1974 to 1976 and found mortality associations with SO_2, but not with TSP (although the model specification for temperature did not address possible lag structure or season). Spix et al. (1993) found significant suspended particle (SP)[1] and SO_2 associations with mortality in Erfurt, East Germany, during 1980 to 1989, with SP remaining significant in simultaneous regressions, despite very high SO_2 levels. Xu et al. (1994) also reported significant mortality associations with SO_2 and TSP (other pollutants not considered) in Bejing, China, but found that SO_2 (not TSP) remained significant in simultaneous regressions.

TSP Studies of Philadelphia

Schwartz and Dockery (1992b) also found a TSP effect in Philadelphia. Subsequent reanalyses of these data have become the primary basis for comparing different modeling

[1]It is not clear as to how the reported SP results might best relate to one or another of other PM indicators, e.g., BS, TSP, PM_{10}, $PM_{2.5}$, etc.

strategies (Wyzga and Lipfert, 1995b; Li and Roth, 1995; Moolgavkar et al., 1995b; Cifuentes and Lave, 1996; Samet et al., 1995).

One reanalysis of the Philadelphia TSP data was reported by Moolgavkar et al. (1995b). This analysis used 1973 to 1988 data on TSP, SO_2, and ozone, with seasons defined by month (December to February for winter, March to May for spring, June to August for summer), and omitting January to February 1973 due to many missing values. The paper reported mortality quintiles and air pollution quintiles by season, combined over all years even though levels changed substantially during the 16-year interval analyzed in the study. The analyses were performed using Poisson regression fitted by GEE methods. The analyses rejected the hypothesis of common temperature and pollution effects in all years and seasons, but not the "Basic" model which used a different intercept for each year with common temperature and pollution effects.

The authors found substantial seasonal differences in air pollution effects on mortality. In summer, there was a statistically significant TSP effect that was little affected by including SO_2 in the model, but reduced to marginal significance by including O_3. In fall and in spring, there was a significant TSP effect that was reduced to non-significance by including SO_2, but actually increased when O_3 was included in the model. In winter, there was a significant TSP effect, but the effect disappeared when SO_2 (which was highest during winter) was included in the model, but little affected by including low winter O3 levels in the model. The RR for 100 $\mu g/m^3$ was about 1.05 in each season when TSP was the only pollutant in the model. This analysis is discussed in more detail in Section 12.6.

Another recent analysis of Philadelphia TSP data has been presented by Cifuentes and Lave (1996). These authors used the more recent time series from 1983 through 1988. The relationship between mortality and air pollution was explored for sensitivity to co-pollutants and weather variables, season, age group, and place of death. These analyses were particularly noteworthy because they also explored nonlinearities in the concentration-response function that could be characterized by piecewise linear models. The models were not, however, "threshold" models in the strictest sense. There were also extensive explorations of the prematurity of death for the periods of time of a few days accessible to daily time series data.

Cifuentes and Lave (1996) used log-linear and Poisson regression models. Time series correlation structure was not specified, except to note that missing values in the air pollution

records were imputed by predictions from a regression model. The air pollutants of interest were TSP, SO_2, and O_3. The mortality regression model predictors considered included the daily averages of the three pollutants or daily maximum hourly values of SO_2 or O_3 across several monitors in Philadelphia county. For TSP, monitor 03 was more predictive than monitor 04 or the average across all monitors, and same day or 1-day lag moving averages were most predictive. For SO_2, the same-day daily average was more predictive than the daily maximum or lagged values. For O_3, the average of the daily maxima of the current and previous day was most predictive. The air pollution concentration metric that best predicted mortality was used for each pollutant. The authors found that TSP was statistically significant even when all three pollutants were included in the model. The SO_2 coefficient was significant alone, but decreased markedly when TSP was included in the model. O_3 was marginally significant even when all three pollutants were included. The results were relatively insensitive to specification of the weather model.

Just as in Moolgavkar et al. (1995b), Cifuentes and Lave (1996) found that there were some important seasonal differences. During winter, TSP was less significant than SO_2, and when both pollutants were included in the model, neither was significant, which may reflect the relatively higher correlation between TSP and SO_2 during these Philadelphia winters. However, the TSP coefficient was relatively stable across the other seasons, and significant in spring and summer, whereas SO_2 was significant only in winter and only without TSP in the model.

As noted in Section 12.2, there are several possible concentration-response function specifications that allow evaluation of possible threshold or break point values. One method is to test if the regression coefficients are not significantly different when the data are broken into two separate parts at a specified cutpoint concentration. A second approach combines both fractions of the split data and assumes that there is a linear relationship with a possibly different regression coefficient in each segment. There appear to be different regression regimes for data split at TSP concentrations of about 90 to 100 $\mu g/m^3$. However, the regression coefficient at concentrations less than about 50 to 60 $\mu g/m^3$ may be larger than the coefficient for higher concentrations, which is the opposite of a "threshold" effect, although the coefficients are poorly estimated with this reduced range of concentrations and smaller number of daily observations. These analyses suggest that the actual relationship may be more complicated than a simple

piecewise linear model, possibly due to a more complex nonlinear relationship involving copollutants or other covariates.

The potential for mortality displacement (harvesting) was examined in different ways. One method was to look at mortality autocorrelation coefficients. Total mortality showed a negative correlation at lag 2 days, and "deaths outside of hospital" inpatients had negative autocorrelation for lags 1 and 2 days. This is consistent with depletion of a potentially susceptible population by acceleration of death by 1 or 2 days, but is not a strong demonstration of the hypothesis.

A much more detailed analysis was based on the definition of "episodes" by Cifuentes and Lave (1996). Episodes are contiguous periods of time in which pollution levels tend to be relatively elevated. They identified more than 100 such 3-day "episodes" during the 6 year period. Positive residuals (excess mortality) during the episode and negative residuals after the episode suggest displacement of mortality during that episode. The authors estimate that from 37% to 87% of the adult deaths that occur during the episode may have been displaced by a few days as a result relative to the pollution exposure episode, and that alternative explanations such as unusual weather events cannot account for the mortality deviations observed during that period of time. This hypothesis and the analytical methods used to test the hypothesis require further study.

Health Effects Institute Analyses (Samet et al., 1995)

An extensive series of reanalyses of air pollution mortality data has been carried out by Samet et al. (1995) as part of the Health Effects Institute study on particulate matter and health. These reanalyses involved reconstruction of databases using data provided by several investigators (D. Dockery, D. Fairley, S. Moolgavkar, A. Pope, J. Schwartz) that would allow evaluation of their published daily time series analyses for Philadelphia, St. Louis, Eastern Tennessee (Harriman-Kingston), Utah Valley, Birmingham, and Santa Clara. A number of new statistical methods were developed for fitting Poisson time series regression models using Generalized Estimating Equation (GEE) techniques. The purposes of the reanalyses of Philadelphia data for 1973 to 1980 included testing the sensitivity of the results to alternative model specifications for temperature and dewpoint, for TSP and SO_2 (singly and jointly), and for effects of season, lag structure, and temporal correlation.

The reanalyses largely confirmed the results obtained by the original investigators. Positive relationships were found between the PM index (TSP for Philadelphia, COH for Santa Clara, PM_{10} for the others) and mortality, and the resulting estimates were statistically significant except for Eastern Tennessee.

The sensitivity analyses for Philadelphia have added important new information to our understanding of the relationship between mortality and TSP when adequate data on copollutants are available, in this case for SO_2. As noted in the methodology discussion in Section 12.2, the analysis of copollutants in every other study has assumed an additive linear model in which each pollutant has an additional linear effect on excess mortality. While the validity of the linearity assumption has been examined in some studies using smooth nonparametric functions for the concentration-response model for a single pollutant, or using quartiles or quintiles of the air pollution variable as separators of categorical dummy variables, no other analysis of multiple pollutants has examined these two assumptions. Samet et al. (1995) used two-dimensional smoothing functions of TSP and SO_2 fitted to total mortality after adjustments for temperature, dew point, and time trends. Seasonality was controlled by indicator variables in the whole-year data set, and by fitting separate models for each season.

The results showed that, while segments of the TSP-SO_2 response surface were approximately linear, the concentration-response surface for both pollutants was clearly neither linear nor additive. There were intervals of the surface where there was little increase with respect to SO_2, but a large increase in excess mortality with increasing TSP; conversely there were ranges of TSP and SO_2 that showed a large increase in excess mortality with increasing SO_2 and little relationship to TSP, especially in winter. This demonstrates at least one case in which standard approaches to modeling response to multiple pollutants can be highly misleading. Attempts to interpret the effects of including one pollutant in the model on estimates of the regression coefficient or relative risk attributed to another pollutant have been based on an assumed linear relationship. While multicollinearity diagnostics can be informative in separating the effects of correlated pollutants in linear models, they may not be diagnosing the problem when the model is itself misspecified in terms of both the shape of the concentration-response and the interaction(s) among the multiple pollutants. This analysis sounds a cautionary note on the interpretation of published results about the sensitivity of RR estimates when

multiple pollutants are used in a model. The interrelationships of Philadelphia TSP and SO_2 by season are discussed further in Section 12.6.

The relationship between Philadelphia mortality and some potentially confounding pollutants has recently been reexamined by Samet et al. (1996a). They fitted models for total mortality, cardiovascular mortality, respiratory mortality, and mortality for other non-external causes, for the period 1974 to 1988. Models were fitted for whole-year data, using adjustments for weather, season, time trends, and for five pollutants: TSP, SO_2, O_3, NO_2, and CO. The results discussed in Section 12.6.2 are for whole-year total mortality with adjustments for averages of current-day and previous-day pollutant concentrations, and for a lagged CO variable denoted LCO that includes the two-day average CO from 3 and 4 days earlier as a predictor of total mortality in a Poisson regression model. They report results from their models somewhat differently than in this document, as the percent increase in mortality per increase in inter-quartile range (denoted IQR) of the pollutant. While we have established standard increments for TSP and SO_2, we have not defined standard increments for the effects of the other pollutants. In general, they find a statistically significant TSP effect when TSP, SO_2, O_3, NO_2, and LCO are all included in the model, with an excess mortality of about 1.06 percent for an IQR of 82.0 - 47.5 = 34.5 $\mu g/m^3$, or RR = 1.031 per 100 $\mu g/m^3$ TSP. The TSP effect is smaller (RR = 1.022) and only marginally significant when only SO_2 is included, slightly smaller (RR = 1.03) and statistically significant when only O_3 is included, and larger when other copollutants are included. See Section 12.6.2 for a more complete discussion.

Overall, qualitatively examining the recently conducted KM, BS, and TSP time-series studies summarized in Table 12-2 reveals that these various PM metrics are typically associated with mortality in most of the studies. The strength and interpretation of that association can vary depending on the number of other pollutants included and on the way they are considered in the analysis. In the above discussed cases where more pollutants were considered, other pollutants were often found to also be associated with mortality, sometimes less strongly and sometimes more strongly than for the PM metric. Moreover, in the cases where the correlations among the significant pollutants were reported, it was consistently found that the PM metric was correlated with these other pollutants. Thus, although these various analyses are strongly supportive of an ambient air pollution effect on mortality throughout the world and are generally consistent with the hypothesis of a PM effect on mortality, they are of limited usefulness in trying to

quantitatively assess PM mortality associations i.e., as a relative risk increases per μg/m^3 increase in thoracic particles (PM_{10}) or fine ($PM_{2.5}$) or coarse ($PM_{10-2.5}$) fractions of PM_{10}. Several studies that are more useful for devising such quantitative relationships are highlighted next.

PM_{10} Studies for the Utah Valley

Table 12-2 includes summaries of some recently reported PM_{10}-mortality studies, where PM_{10} was directly measured or calibrated for the site. Among these was a study of total, respiratory, and cardiovascular mortality in Utah County, UT during 1985 to 1989 (Pope et al., 1992). In this study, the various daily counts of mortality were regressed on the 5-day moving average PM_{10}, as well as on temperature, humidity, a time-trend term, and random year terms. While only one site was used to represent the whole county's PM_{10} level, comparisons with two other PM_{10} sites indicated spatial consistency (correlation between sites $\geq$ 0.95). Autoregressive Poisson methods were used because of the low total mortality counts (mean = 2.7/day) in this relatively small population (260,000). Using this model, a significant positive association was found between total non-accidental mortality and PM_{10}, and the authors concluded that a 100 μg/m^3 increase in the 5-day average PM_{10} concentration was associated with a 16% increase in mortality. Analyses presented indicate that the use of concurrent day PM_{10}, rather than a 5-day average, would have resulted in an effect estimate roughly half that reported in terms of the 5-day average PM_{10} (in deaths per μg/m^3). A "control" disease category (i.e., one unlikely to be affected by air pollution) was not considered per se. However, deaths due to causes other than respiratory or cardiovascular were considered, and found not to be associated with PM. Respiratory deaths were more strongly associated with PM_{10} than any other cause. These results support the biological plausibility of a PM-mortality association. Also, the PM_{10}-mortality association was found for PM levels well below the existing 24-h average PM_{10} standard of 150 μg/m^3. The authors dismiss other air pollutants as having negligible influence by comparing them to their respective present air quality standards without directly modeling the possibility that other (correlated) air pollutants might also influence mortality. On the other hand, Pope (1994) reported that PM_{10}, and SO_2 were only weakly correlated (r = 0.19), acid aerosol (H^+) levels were below 8 nmoles/m^3, and the introduction of O_3 into the model actually strengthened the PM_{10} association.

A reanalysis of deaths in Utah Valley, UT, from 1985 to 1992 was carried out by Lyon et al. (1995). The data were extensively categorized by year, season, cause, age, and place of death. Based on quintile plots, the authors concluded that excess mortality increased steeply at about 50 $\mu g/m^3$ and consequently used only a dichotomous indicator of PM_{10} greater than 50 $\mu g/m^3$, rather than any linear or nonlinear function of PM_{10}. No other pollutants were used, and the only meteorological variable used in the model was minimum daily temperature. Relative risk (called rate ratio) was calculated from a Poisson regression model without time series structure adjustment by GEE. However, a linear time trend was used to adjust for decreasing mortality rates over the years. The authors found an apparently random pattern of increased RR, by year, season, age, cause, and place of death. Among their results, they noted the following: strongest effect in spring, not winter; largest contribution to excess mortality from age 75 and over dying in hospital; largest RR for ages 15 to 59 dying at home from cancer; increased RR for sudden infant death syndrome. The choice of a 5-day mean PM_{10} as the exposure metric was based on an earlier study (Pope et al., 1992). However, dichotomizing the PM_{10} metric at 50 $\mu g/m^3$ may have cost a great deal of useful information, possibly including a substantial exposure measurement error or misclassification problem. Since this PM_{10} metric cannot be scaled to RR increments over other ranges of values, we were not able to include this study in the subsequent tables of this section. However, the authors estimate an excess mortality of 4% for PM_{10} above 50 $\mu g/m^3$, roughly consistent with other studies.

The Utah Valley mortality data have also recently been reanalyzed by Pope and Kalkstein (1996). This reanalysis evaluates a number of alternative approaches to controlling for weather-related variables and time trends, including nonparametric smoothing and the use of Kalkstein et al. (1987) Temporal Synoptic Index (TSI) climatological categories. The weather data from the Salt Lake City airport for 20 preceding years were used to create 19 categories of air mass types, each typically of several days' duration. The TSI and related methods are described in Section 12.6. The TSI method is essentially an objective procedure, based on clustering of principal components of 7 weather variables measured 4 times per day. The TSI categories are often closely identified with temperature and humidity differences that characterize different seasons, which allows a potentially more flexible approach than defining seasons by fixed calendar dates. Poisson regression analyses were performed on mortality data for April 7, 1985 (when PM_{10} monitoring began) through December 31, 1989. A large number of models were fitted to the

data, some of which are discussed in more detail in Section 12.6. Relative risk estimates for PM_{10} showed some sensitivity to model specification for time trends, but were consistently significant when long-term time trends were appropriately controlled, as by use of LOESS smoothers. Typical RR values were about 1.06 to 1.08 per 50 $\mu g/m_3$ PM_{10} for total mortality, consistent with earlier studies, and higher for death from cardiovascular causes (1.08 to 1.10) and for death from pulmonary causes (1.12 to 1.20).

The results showed very little sensitivity to variations in methods for controlling for weather-related effects, provided the methods had sufficient flexibility to model changes. Both the use of TSI categories and the adjustments using LOESS smoothers of temperature and dewpoint provided similar estimates of PM_{10} effects. While larger differences might be observed in communities with more variable climate conditions, this study suggests that the exact form of the weather model may not have a large effect on pollution estimates within a range of different methods. Additional comparisons in other communities are needed to evaluate the sensitivity of PM estimates to different methods of adjustment for weather.

PM_{10} Studies: St. Louis, MO and Kingston-Harriman, TN

Dockery et al. (1992) investigated the relationship between multiple air pollutants and total daily mortality during one year (September 1985 through August 1986) in two communities: St. Louis, MO; and Kingston/Harriman, TN and surrounding counties. In the latter locale, the major population center considered was Knoxville, TN, some 50 Km from the air pollution monitoring site employed. Total daily mortality in each study area was related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temperature, dew point, and season using autoregressive Poisson models. In St. Louis, after controlling for weather and season, statistically significant associations were found with both prior day's PM_{10} and $PM_{2.5}$, but not with any lags of the other pollutants considered. In the Kingston/Harriman vicinity, PM_{10} and $PM_{2.5}$ approached significance in the mortality regression, while the other pollutants did not. In both cities, very similar PM_{10} coefficients are reported, implying a 8 to 9 percent increase in total mortality per 50 $\mu g/m^3$ of PM_{10}. While autocorrelation was accounted for, seasonality was only addressed by season indicator (dummy) variables, which could not address any within-season long wave influences. Also, in both places, only one daily monitoring station was employed to represent community exposure levels, and no information regarding the representativeness of these sites was provided

(e.g., correlations with other sites' data). Thus, using mortality data for Knoxville, TN (50 km from the Kingston/Harriman, TN monitoring site at which PM was measured) in the PM-mortality analysis raises questions about the representativeness of the exposure estimates used. Furthermore, the number of days for which pollution data are available for time-series analyses is limited in this data set, especially for H^+ (e.g., only 220 days had H^+ values at the St. Louis site). As stated by the authors: "Because of the short monitoring period for daily particulate air pollution, the power of this study to detect associations was limited." Nevertheless, despite these limitations, consistent PM_{10} coefficients were found for each of these two cities.

PM_{10} Studies: Birmingham

Total mortality-PM_{10} relationship in Birmingham, AL during August, 1985 through December, 1988 were evaluated by Schwartz (1993a). Poisson modeling was used to address small count effects (mean mortality = 17.1 deaths/day), season was addressed by the inclusion of 24 sine and cosine terms having periods ranging from 1 to 24 mo, and weather was modeled using various specifications of temperature and relative humidity. Autocorrelation was addressed using autoregressive parameters, as required, and day of week dummy variables were also included. In these analyses, significant associations were found between total daily mortality and the average of the three prior day's PM_{10} concentration. It was noted that averaging fewer days weakened the PM_{10}-mortality association, consistent with the expectation that multiple day pollution episodes are of the greatest health concern. The analysis did not look at any other pollutants, making it impossible to directly assess whether the association noted is due to PM_{10} alone or also in part to some other collinear pollutant (e.g., SO_2) not considered in the analysis. However, a variety of modeling approaches gave similar results, as did eliminating all days with PM_{10} >150 $\mu g/m^3$, indicating that the PM-mortality associations noted are not dependent on model choice or limited to elevated pollution days only.

PM_{10} Studies: Toronto

Özkaynak et al. (1994) related total daily mortality in Toronto, Ontario during 1972 to 1990 to daily PM_{10}, TSP, SO_4, CO, O_3, temperature, and relative humidity. A 19-day moving average equivalent high-pass filter was used to prefilter out long-wave cycles in the data and to

reduce autocorrelation. OLS regression was employed, as the distribution of mortality data tend toward the normal in larger cities such as Toronto (mean deaths = 40/day) once seasonal cycles are removed. In this dataset, 6,303 PM_{10} daily values were estimated based on TSP, SO_4, COH, visibility (i.e., Relative Humidity corrected B_{ext}, the extinction coefficient derived from airport visibility observations), and temperature data, using a model developed from 200 actual PM_{10} sampling days during the study period. This limits the usefulness of the results for distinguishing PM_{10} in the analyses, as it is derived from other PM metrics and from variables which may themselves be causally related to mortality (e.g., temperature). For example, estimated PM_{10} is correlated at r = 0.95 with TSP, and r = 0.27 with temperature. In the analyses, all pollutants considered were significantly associated with daily mortality. The simultaneous regression of total mortality on both O_3 and PM_{10} yielded significant coefficients for each. The PM_{10} mean effect (at 41 $\mu g/m^3$) was reported to be 2.3% of total mortality. However, the authors found that it was not possible to separate the PM_{10}-mortality association from that for other PM metrics considered.

PM_{10} Studies: Los Angeles

Kinney et al. (1995) investigated total daily mortality in Los Angeles, CA during 1985 to 1990 (mean = 153 deaths/day), relating it to PM_{10}, O_3, CO, temperature, and relative humidity to assess the sensitivity of the PM-mortality association to model type and model specification. Pollution data were averages of all sites available (e.g., 4 for PM_{10} and 8 for O_3 and CO), after first filling in missing days at each site based on available data from other sites (thereby addressing error from day to day variation in site availability). Although the data were collected over 6 years, the PM_{10} sampling was conducted only every sixth day; so, only 364 days could be included in the analysis, limiting its power to detect associations. Poisson models were used which addressed seasonal long wave influences by including sine and cosine terms ranging in periodicity from 1 to 24 mo in periodicity; OLS and log-linear models were also considered. Weather was modeled initially by including only same-day maximum temperature and relative humidity in regressions, but sensitivity analyses also considered dummy variables for extreme temperature and up to 3-d lags of all weather variables. Winter and summer were also modeled separately. In these various analyses, PM_{10} was generally found to be significantly associated with mortality after controlling for weather and season, with a relative risk (RR) estimate of

approximately 1.05 (CI = 1.0 to 1.10) reported for a 100 μg/m^3 increase in PM_{10}. Durbin - Watson (DW) statistics indicated only modest autocorrelation in these models (1.8<DW<2.0). The PM_{10}-mortality association was found to be only mildly sensitive to modeling method. However, CO was also significantly associated with mortality, and the simultaneous inclusion of either CO or O_3 to the PM_{10} model lowered the significance of PM_{10} in the model noticeably, but affected the coefficient less. The correlations among the pollutant's coefficients in this model were, however, significant ($r_\beta(PM_{10}\text{-}CO) = -0.4$; $r_\beta(PM_{10}\text{-}O_3) = -0.5$). Therefore, despite the effort made to maximize the quality of the exposure estimates and to appropriately address the statistical and multi-pollutant aspects of the analysis, the PM-mortality association was not completely separable from other copollutants. In this sense, these results are quite similar to those found previously for L.A. (Kinney and Ozkaynak, 1991).

PM_{10} Studies: Los Angeles and Chicago

Ito et al. (1995) considered total daily mortality during 1985 to 1990 in Los Angeles, CA (mean = 153 deaths/day) and Chicago, IL (mean = 117 deaths/day) in their investigation of the role of monitoring site choice on PM_{10} health effects analyses results. Poisson models were used which included four sine and cosine terms ranging from 1 to 24 mo in periodicity to control for season, day of week dummy variables, a linear trend term, and temperature. In each city, multi-site averages were computed for each pollutant considered (PM_{10} and O_3) after missing day's values were estimated at each site from other data available for that day. Also, simple daily averages of all available data were computed (without filling missing), and each site's raw data were also individually analyzed. The average of the multiple sites' PM_{10} was found to be significantly associated with total mortality in each city after controlling for season, temperature, and O_3. However, while the O_3 coefficient was only moderately correlated with the PM_{10} coefficient ($r_\beta = -0.2$), other potentially more correlated pollutants (e.g., CO, SO_2, or NO_2) were not considered in this basic model specification. Also, the size and significance of the PM_{10} coefficient in mortality regressions varied widely among the individual sites. The authors concluded that: "Thus, identification of a single causal pollutant, based simply on the strength of association with a health effect outcome without evaluation of attenuation/enhancement due to

random/systematic errors in exposure estimates, may be misleading." Dividing the data by season also diminished the significance of PM_{10} in mortality regressions, as would be expected due to reduced sample size. However, the PM_{10} coefficient was not as affected by season-specific analyses, indicating consistent associations throughout the year. Overall, multi-site averaging and larger sample sizes were shown to strengthen the PM_{10}-mortality association, but the results (and the fact that a very basic model specification was employed) leaves open the possibility that other co-pollutants or more elaborate weather specifications could account for part of the Chicago PM_{10} association with daily mortality.

PM_{10} Studies: Chicago/Cook County

Styer et al. (1995) considered total, respiratory, circulatory, and cancer deaths in Cook County, IL (Chicago). The mean number of total, respiratory circulatory, and cancer deaths in Cook County were 117 for all nonaccidental causes, 83 of them elderly (age 65 and over), 10 from respiratory causes (ICD 9 codes 11, 35, 472 to 519, 710.0, 710.2, 710.4), 56 from circulatory causes (ICD 9 codes 390 to 459), 28 from cancer (ICD 9 codes 140 to 209) per day. They also broke down total mortality by race and by sex. Exposure metrics were based on one daily station and up to 12 measurements per day from other monitoring stations in Cook County. Models were fitted using Poisson regression, with adjustments for mean daily temperature, specific humidity, and average daily pressure, but with no other air pollutant in the model. Pollen counts and other meteorological variables were evaluated but did not significantly improve one fitted model; semi-parametric and parametric models for PM_{10} were tested, with lags up to 5 days. Seasonal adjustments were significant.

The overall PM_{10} effect in Cook County was found to be statistically significant overall. However, Spring and Autumn showed significant PM_{10} effects, whereas Winter and Summer did not. Elderly mortality had twice the excess risk of total mortality. Respiratory deaths in Cook County had nearly three times the response to PM_{10} as total mortality, but was only marginally significant. The best PM_{10} predictor for most of the Cook County analyses performed by Styer et al. (1995) was a 3-day moving average (lags 0, 1, 2). While other PM_{10} lags were evaluated, no other pollutants were tested. The total mortality RR for 50 $\mu g/m^3$ PM_{10} in Cook County can be estimated as 1.04 (95% confidence interval 1.00 to 1.08) and is consistent with other studies. This study found a statistically significant cancer death effect that was about twice as high as the

PM_{10} effect on total mortality. The finding of a cancer death effect in a short-term study is unexpected and differs from the finding of no cancer effect in a TSP study in Philadelphia (Schwartz and Dockery, 1992a); thus, it may be a chance effect. However, cancer effects were identified in all three of the long-term prospective cohort studies discussed in Section 12.4.

PM_{10} Studies: Salt Lake County, Utah

Styer et al. (1995), in the same paper reporting on their Cook County findings, also described results obtained from analyses of PM_{10} relationships to elderly total daily mortality in Salt Lake County, UT. Date from two daily PM_{10} stations in Salt Lake County served as exposure metrics included in models fitted using Poisson regression, with adjustments for mean daily temperature, specific humidity, and average daily pressure. No other pollutants besides PM_{10} were considered in the models. Even without other pollutants in the models, Styer et al. (1995) reported finding no effect of PM_{10} on elderly mortality in Salt Lake County, UT.

PM_{10} Studies: Santiago, Chile

Ostro et al. (1996) considered total, respiratory, and cardiovascular daily deaths (mean = 55, 8, and 18 deaths/day, respectively) in Santiago, Chile during 1989 to 1991, examining their relationship to ambient PM_{10}, O_3, SO_2, and NO_2, and to daily minimum and maximum temperature and humidity. To improve exposure estimate representativeness, multiple sites' daily data were averaged for each pollutant (e.g., 4 sites for PM_{10}), though the maximum from all 4 PM_{10} sites for each day was also considered in some analyses. In this work, most regressions employed the log of PM_{10}, as it showed the highest associations with total mortality in exploratory analyses.

OLS regression was employed for most total mortality regressions because a test of normality was not rejected for the total mortality data, though Poisson regressions were used for cause-specific analyses in view of their lower daily counts. Also, sensitivity analyses were conducted for various model types: the total mortality RR of the mean PM_{10} concentration (115 $\mu g/m^3$) ranged from 1.04 to 1.09 (1.12 with a 3-day average mean PM_{10} employed). Seasonal influences were also addressed by various methods, including seasonal stratification, the inclusion of sine/cosine trigonometric terms for 2.4, 3, 4, 6, and 12 mo periodicities, prefiltering, and the use of various non-parametric fits of temperature: the PM_{10} RR estimate ranged from

1.04 to 1.11, with the lowest mean PM_{10} risk provided by the OLS model with 5 trigonometric terms included (RR = 1.04). Investigations of mortality by-cause and age found the strongest PM_{10} associations for respiratory-specific deaths (RR = 1.15) and for the elderly (RR = 1.11). Other pollutants were also considered separately and simultaneously with PM_{10} in a total mortality regression which also contained 36 dummy variables (one for each month of the study). In this model, the individually significant pollutants were: log(PM_{10}) (RR at mean = 1.05 ; CI = 1.01 to 1.08); SO_2 (RR at mean = 1.01; CI = 1.00 to 1.03), and; NO_2 (RR at mean = 1.02 ; CI = 1.01 to 1.04). Thus, all three pollutants had similar levels of significance in this model, but only log(PM_{10}) stayed significant in multi-pollutant regressions. The intercorrelations of the various pollutants' coefficients were not reported, but they were likely high, given that the pollutants themselves were highly intercorrelated over time, e.g., r(PM_{10}-NO_2) = 0.73. Overall, these results suggest that, of the pollutants considered, PM_{10} is the air pollutant most strongly associated with mortality in this setting; and the sensitivity analyses suggest that the elderly with respiratory diseases were most susceptible to ambient air pollution effects.

Time Series Analyses Comparing PM_{15}, Fine, and Coarse Thoracic Particles

The daily time series data from the Six City Study has recently been reanalyzed (Schwartz et al., 1996) using statistical methods for Poisson data similar to those used in most other recent studies. This study extended the Dockery and Schwartz (1992) analyses to four additional regions, and also included separate analyses for fine particles ($PM_{2.5}$, denoted FP) coarse fractions particles (PM_{15} - $PM_{2.5}$ denoted CP), sulfates and acidity. The PM_{15} and $PM_{2.5}$ studies were carried out between 1979 and 1987, with daily samples ranging from 1,140 in Boston up to 1,520 in Steubenville. Poisson time series regression models were fitted, with statistical adjustments for time trends, temperature, and dew point using nonparametric smoothers in a generalized additive model. Since 62% of the $PM_{2.5}$ daily samples did not have a previous-day $PM_{2.5}$ measurement, lag structures were not examined. However, the exposure metric for each day was assumed to be the mean of the available non-missing current or previous day $PM_{2.5}$ values, which increased the total data set used from 7,436 to 12,055 observations. The acid aerosol measurements were, however, only available for 159 to 429 days in each of six regions. No $PM_{2.5}$ or PM_{10} analyses were presented based only on the reduced subset of days for which

H^+ data were available, which would have allowed more specific comparisons of the goodness of fit of H^+ with other PM indices.

The results for PM_{15} showed that very similar increases in daily mortality associated with thoracic particles occurred in five of the six cities, with RR ranging from 1.030 to 1.061 per 50 $\mu g/m^3$ PM_{15} except in Topeka, which had negative excess PM_{15} risk. The results were statistically significant except in Portage and Topeka.

Furthermore, of much interest, there were very similar increases in daily mortality associated with fine particles in all six cities, with RR ranging from 1.020 to 1.056 per 25 $\mu g/m^3$ $PM_{2.5}$. The results were statistically highly significant in Harriman-Kingston, St. Louis, and Boston, and nearly so in Portage and Steubenville. The effect size was similar in magnitude, but not significant in Topeka.

In contrast, coarse fraction particles (PM_{15} - $PM_{2.5}$) showed small and non-significant RR values, except for Steubenville (RR = 1.061 per 25 $\mu g/m^3$ CP). Excess risk was again negative for Topeka, and RR ranged from only 1.005 to 1.025 per 25 $\mu g/m^3$ for the four other cities. Based on these results, the authors concluded that, in most cases, associations between excess mortality and inhalable particles appears to be derived mainly from the fine particle fraction. Even in the case of Steubenville, the significant coarse particle-mortality associations may be due to fine partilce effects, given that the coarse particle levels were highly correlated with $PM_{2.5}$ concentrations.

When data for all six cities were combined, the combined estimate of the effects of PM_{15} and $PM_{2.5}$ were even more highly significant, with $PM_{2.5}$ definitely more predictive than PM_{15}. The combined estimate for CP was marginally significant, probably reflecting the significant contribution of Steubenville. Similar estimates were carried out for sulfates and for acid aerosols. The sulfate component was a statistically significant predictor of excess mortality, although less so than either PM_{15} or $PM_{2.5}$. H+ was not significant, even with 1,621 days of data in four cities, but the power of the H^+ analyses was lower than for the other PM indices. Thus, although the anomalous Steubenville CP findings cannot be entirely ignored, the overall pattern of results most clearly implicates fine particle indicators as being most strongly and consistently associated with increased daily mortality in the Six-City Study database.

The authors also evaluated a possible nonlinear relationship by considering only days with $PM_{2.5}$ less than 25 or less than 30 $\mu g/m^3$. The fitted log-linear relationship was larger in

magnitude than when all $PM_{2.5}$ days were included, RR = 1.056 (CI 1.035 to 1.077) per 25 $\mu g/m^3$ on days with $PM_{2.5} < 25$ $\mu g/m^3$.

Additional analyses explored specific causes of death. The excess risk of death by ischemic heart disease associated with $PM_{2.5}$ was about 40% higher than for all-cause nonexternal mortality, and more than twice as high for death by pneumonia and by COPD.

12.3.1.2 Short-Term PM_{10} Exposure Associations with Total Daily Mortality: Syntheses of Studies

Most of the studies summarized in Table 12-2 and discussed in more detail above considered daily mortality in the entire population (i.e., all ages) and due to all causes, although some also considered sub-populations. Considering all of these studies in one overall assessment of PM effects on mortality is not a straightforward task, given the variety of models and model specifications employed but, as noted above, this has been attempted previously. Table 12-3 presents intercomparisons of PM-daily mortality results based on of two recently published summaries of the PM literature which attempted to convert all results to a PM_{10}-equivalence basis and to provide quantitative intercomparisons (Ostro, 1993; Dockery and Pope, 1994b). As also noted above, other such syntheses have been conducted using TSP as the reference PM metric (Schwartz, 1992a, 1994b), but many of the same studies were considered in thetwo PM_{10}-equivalent summaries, so the TSP-equivalent results are not tabulated here.

The results presented in Table 12-3 suggest about a 1 percent change in acute total mortality for a 10 $\mu g/m^3$ change in PM_{10}, but the estimates range from 0.3 to 1.6% (i.e., a factor of 5). It is important to note that other air pollutants have generally not yet been addressed in reaching these reported PM coefficients. While most of the 95% confidence intervals (CI's) of the PM estimates overlap, CI's of the highest and lowest estimates do not overlap, indicating significant differences between these estimates. The effects indicated for a 10 $\mu g/m^3$ change cannot be consistently converted to other PM increments (e.g., 50 or 100 $\mu g/m^3$ PM_{10}), as differences in model specification (e.g., linear versus log models) will cause them to differ in their conversions to other particle concentration levels. Reasons for the approximately five-fold effect estimate difference noted among studies are not obvious from the information provided by these references, but one factor appears to be the PM exposure averaging time, as estimates using multiple day PM_{10} averages are all 1% or higher. This is not unexpected, given that (in the absence of a strong harvesting effect) any lagged effects from prior days of PM_{10} exposure would be added to the effects estimate when a multi-day average is employed, increasing the estimated effect on a per $\mu g/m^3$ basis. Also, PM coefficient variation can be expected, given that the composition (and, therefore, toxicity) of the PM, as well as the population make-up, in each city can be expected to differ. Moreover, the conversions from other PM metrics to PM_{10} must necessarily introduce additional uncertainty. This is made apparent here when comparing the estimates for Santa Clara, CA from the two listed references, each having its own somewhat

different estimate of the equivalent PM_{10} and of the PM_{10} effect. Although not all of these results may therefore be the most appropriate available for quantifying a PM_{10} effect, they do indicate a consistent association between acute PM exposure and increased daily mortality. Moreover, the by-cause results also reported in these summaries indicate that PM effect estimates are greater for respiratory causes, lending support to the biological plausibility of the PM associations.

In an attempt to better quantify daily PM_{10}-total acute mortality associations indicated by the above discussions, Table 12-4 presents a summary of the total mortality relative risks (RR) of a 50 $\mu g/m^3$ increase in PM_{10} estimated from nine studies reviewed above which employed PM_{10} data in their analysis of total mortality data (or which had on-site PM_{10} reference data to convert other PM metrics with more certainty). This selection of studies does not mean to dismiss the other studies discussed above as less important; the studies selected, however, can most readily be intercompared and referred to the present PM_{10} standard. The RR's calculated were based upon a 50 $\mu g/m^3$ increase above the mean PM_{10}, which is the order of magnitude of the difference between the maximum and mean in these cities and roughly approximates the estimated effects of a typical day experiencing an exceedance of the present PM_{10} standard, relative to the average case. This is important to note, because in non-linear models such as were often employed in the studies in Table 12-3, the RR estimate associated with a given $\mu g/m^3$ PM_{10} increase will vary depending upon the baseline concentration to which it is added.

From the results presented in Table 12-4, it is apparent that these studies generally have yielded at least marginally significant PM_{10} coefficients, but that the resultant excess risk estimates vary by a factor of five across these studies (from 1.5% to 8.5% per 50 $\mu g/m^3$ for the year-round analyses). The mean and maximum PM_{10} concentration data are noted for each study. If the PM_{10} coefficient increased as the mean level of PM_{10} decreased, then confounding or non-linearity might be suspected. However, the data presented indicate that the variability in coefficients is not a function of PM_{10} level, as sites with high or low PM_{10} concentrations can report either high or low RR's. In Table 12-5, an attempt is made to concisely summarize the statistical methodology characteristics of each study, in order to

TABLE 12-4. COMPARISON OF RELATIVE RISK (RR) ESTIMATES FOR TOTAL MORTALITY FROM A 50 $\mu g/m^3$ INCREASE IN PM_{10}, USING STUDIES WHERE PM_{10} WAS MEASURED IN THE UNITED STATES OR CANADA[a]

Study	Reference	PM_{10} ($\mu g/m^3$)		Other Pollutants In Model	Lag Times, d	RR per 50 $\mu g/m^3$	95 Percent Confidence Interval
		Mean	Maximum				
Utah Valley, UT	Pope et al. (1992)	47	297	None	≤ 4 d	1.08	(1.05, 1.11)
	Pope and Kalkstein (1996)	47	365	None	≤ 4 d	1.07	(1.02, 1.12)
Birmingham, AL	Schwartz (1993a)	48	163	None	≤ 3 d	1.05	(1.01, 1.10)
St. Louis, MO	Dockery et al. (1992)	28	97	None	≤ 3 d	1.08	(1.005, 1.15)
	Schwartz et al. (1996)	31		O_3	≤ 3 d	1.06	(0.98, 1.15)
				None	≤ 1 d	1.03	(1.005, 1.05)
Kingston, TN	Dockery et al. (1992)	30	67	None	≤ 3 d	1.085	(0.94, 1.25)
	Schwartz et al. (1996a)	32		O_3	≤ 3 d	1.09	(0.94, 1.26)
				None	≤ 1 d	1.05	(1.005, 1.09)
Portage, WI	Schwartz et al. (1996a)	18		None	≤ 1 d	1.035	(0.98, 1.09)
Boston, MA	Schwartz et al. (1996a)	24		None	≤ 1 d	1.06	(1.04, 1.09)
Topeka, KS	Schwartz et al. (1996a)	46		None	≤ 1 d	0.98	(0.90, 1.05)
Steubenville, OH	Schwartz et al. (1996a)	46		None	≤ 1 d	1.05	(1.005, 1.08)
Toronto, ON Canada	Özkaynak et al. (1994)	40	96	None	0 d	1.025	(1.015, 1.034)
Los Angeles, CA	Kinney et al. (1995)	58	177	None	1 d	1.025	(1.00, 1.055)
				O_3, CO	1 d	1.017	(0.99, 1.036)
Chicago, IL	Ito et al. (1995)	38	128	O_3, CO	≤ 3 d	1.025	(1.005, 1.05)
Chicago, IL	Styer et al. (1995)	37	365	None	3 d	1.04	(1.00, 1.08)
Chicago, IL	Ito and Thurston (1996)	41	>65[b]	None	≤ 1 d	1.025	(1.005, 1.04)
				O_3	≤ 1 d	1.02	(1.005, 1.035)

[a]Calculated on basis of 50 $\mu g/m^3$ increase, from 50 to 100 $\mu g/m^3$ PM_{10}.
[b]90th percentile.

TABLE 12-5. ADDITIONAL INFORMATION ON TIME SERIES STUDIES OF PM_{10}-MORTALITY CITED IN TABLE 12-4

Study	Reference	Period	Other Pollutants In Model	Lags Addressed		Multiple Methods	Correl. of B's Given	No. of Obs.
				Pollutants	Temp			
Utah Valley, UT	Pope et al. (1992)	1985-1989	None	0-4 d	≤ 1 d	Yes	No	1,436
St. Louis, MO	Dockery et al. (1992)	1985-1986	$PM_{2.5}$, SO_4, H^+, SO_2, NO_2, O_3	≤ 3 d	≤ 1 d	No	No	311
Kingston, TN	Dockery et al. (1992)	1985-1986	$PM_{2.5}$, SO_4, H^+, SO_2, $NO_{2.5}$, O_3	≤ 3 d	≤ 1 d	No	No	330
Birmingham, AL	Schwartz (1993a)	1985-1988	None	0-3 d	≤ 3 d	Yes	No	1,087
Toronto, ON Canada	Özkaynak et al. (1994)	1972-1990	TSP, $PM_{2.5}$, SO_4, O_3, COH, NO_2, SO_2	0 d	0 d	No	No	6,506
Los Angeles, CA	Kinney et al. (1995)	1985-1990	O_3, CO	1 d	≤ 3 d	Yes	Yes	364
Chicago, IL	Ito et al. (1995)	1985-1990	O_3, CO	≤ 3 d	≤ 3 d	No	Yes	1,357
Chicago, IL	Styer et al. (1995)	1985-1990	None	≤ 5 d	≤ 2 d	Yes	No	1,357

determine if any of these factors are important to the variability observed from study to study in the PM_{10} RR estimate. Of all factors examined in this table, the one most consistently present with higher PM_{10} RR's is when other pollutants have not been simultaneously considered in the model. Indeed, those studies which considered PM_{10} both alone and with other pollutants in the model yielded consistently smaller (and usually more marginally significant) PM_{10} relative risks when the other pollutants were simultaneously considered. This influence ranges from roughly a 20 to 50 percent reduction in the excess risk associated with 100 $\mu g/m^3$ in PM_{10} (e.g., in Athens, Greece, the PM_{10} RR declines from 1.07 to 1.03 when other pollutants are considered). However, such a reduction is to be expected when colinear variables are added, and the "true" PM_{10} RR is likely to lie between the single pollutant and multi-pollutant model estimates, provided that the pollutant variables and other covariates are relatively free of measurement error and that the regression model is correctly specified.

Another factor which clearly affected the PM_{10} RR from some of the studies listed in Table 12-4 was the PM_{10} averaging period. Both of the studies which utilized multi-day averages of PM_{10} in their regressions (i.e., Utah Valley, UT and Birmingham, AL) are among the higher RR estimate studies. As discussed above, this would be expected, but the increase indicated for these studies is not as large as might be expected. Indeed, in sub-analyses included by Pope et al. (1992), the PM_{10} mortality risk is indicated to be roughly doubled by using a five day average versus a single day concentration, while sub-analyses presented by Ostro et al. (1996) for Santiago also indicate approximately a doubling in the PM_{10} RR when a 3 day average is considered (i.e., from RR = 1.04 for a single day PM_{10} value to RR = 1.07 for a 3d average PM_{10} value). This may be due to the fact that, since correlation exists over time in the PM_{10} concentrations, the single day concentration is "picking up" some of the effect of multi-day pollution episodes, even though they are not explicitly modeled. Also, most studies show a maximum same-day or one day lag PM-mortality association, with the PM_{10} regression coefficient decreasing on subsequent days.

It appears from Table 12-4 that the total acute mortality relative risk estimate associated with a 50 $\mu g/m^3$ increase in the one-day 24-h average PM_{10} can range from 1.015 to 1.085 in year-round analyses, depending upon the site (i.e., the PM_{10} and population composition) and also upon whether PM_{10} is modeled as the sole index of air pollution. Relative Risk estimates with PM_{10} as the only pollutant index in the model range from RR = 1.025 to 1.085, while the

PM_{10} RR with multiple pollutants in the model range from 1.015 to 1.025. The former range might be viewed as approximating an upper bound of the best estimate, as any mortality effects of co-varying pollutants are likely to be "picked up" by the PM_{10} index, while the multiple pollutant model range might be viewed as approximating a lower bound of the best estimate, assuming that other co-pollutants are controlled for, as the inclusion of highly correlated covariates are likely to weaken the PM_{10} estimate, even if they are not themselves causal. Both estimates should be considered in assessing the potential effects of PM_{10}. Overall, consistently positive PM-mortality associations are seen throughout these analyses, despite the use of a variety of modeling approaches, and even after steps were taken to statistically control major confounders such as season, weather, and co-pollutants, with the 24-h average 50 $\mu g/m^3$ PM_{10} total mortality effect estimate apparently being in approximately the RR = 1.025 to 1.05 range. Comparison of alternative PM exposure indices as well as other pollutants, can also be done using elasticity as a dimensionless index of relative risk (Lipfert and Wyzga, 1995b).

12.3.1.3 Short-Term PM_{10} Exposure Associations with Daily Mortality in Elderly Adults

Of the studies in Tables 12-2 to 12-5 discussed above, only a few directly examined the elderly as a potentially sensitive sub-population. Certainly, since the highest mortality rates are among the elderly, this is a population which surely dominated the total mortality analyses discussed above, and it is therefore logical to assume that the bulk of the total mortality effects suggested by these studies are among the elderly. Also, as noted earlier, during the historic London, 1952 pollution episode the greatest increase in mortality rate was among older citizens and those with respiratory diseases. More recently, an analysis by Schwartz (1994c) of mortality in Philadelphia, PA during 1973 through 1980 comparing mortality during the 5% highest versus the 5% lowest TSP days found the greatest increase in risk of death among those aged 65 to 74 and those >74 year of age (mortality risk ratios = 1.09 and 1.12, respectively, between high and low TSP days). Also, in their time series analyses of Philadelphia daily mortality during this period, Schwartz and Dockery (1992a) found a significantly higher TSP-mortality coefficient (ß = 0.000910 ± 0.000161) for persons older than 65 years of age than for the younger population (ß = 0.000271 ± 0.000206). These coefficients indicated an effect size for the elderly roughly three times that for the younger population (10% versus 3%, respectively, for a 100 $\mu g/m^3$ TSP increase).

In addition, two recent PM_{10} analyses which directly considered the question of PM_{10}-mortality associations among the elderly population (≥ 65 years of age), provide further relevant insights into this question. The first of these two analyses was conducted by Saldiva et al. (1994) during May 1990 through April 1991 in Sao Paulo. Environmental variables considered included PM_{10}, SO_2, NO_x, O_3, CO, temperature, and humidity. PM_{10} was not measured gravimetrically, but rather by beta gauge instrument readings calibrated to mass. Pollutants were considered in the analysis in the form of 2-day moving averages (i.e., averages of the same-day and the prior day's concentration). Monitoring data from multiple sites were averaged for each pollutant (e.g., 8 sites for PM_{10}). Multiple regression models estimated the association between daily mortality and air pollution controlling for month of year, temperature, relative humidity, and day of week. Because of the large number of daily deaths (mean = 63/day), Gaussian regression models were appropriately used for the basic analysis. Poisson models using the generalized estimating equation of Liang and Zeger (1986) were also applied for comparison. Temperature effects were crudely accounted for through the use of three dummy variables ($T < 8\ ^\circ C$; $8\ ^\circ C \leq T \leq 12\ ^\circ C$; $13\ ^\circ C \leq T \leq 18\ ^\circ C$) in the basic model. Regression results indicated that, when studied separately, PM_{10}, SO_2, NO_x, and CO were all significantly associated with mortality. In a simultaneous regression of mortality on all pollutants, however, PM_{10} was the only pollutant that remained significant. In fact, the PM_{10} coefficient actually increased, suggesting confounding among these correlated pollutants. Thus, as noted by the authors, "the close interdependence exhibited by the concentrations of measured pollutants suggests that one has to be cautious when ascribing to a single pollutant the responsibility of causing an adverse health effect". Nevertheless, multiple regression models, including those considering all pollutants simultaneously, consistently attributed the association found with mortality among the elderly to PM_{10}. The reported PM_{10} relative risk (RR = 1.13 for a 100 $\mu g/m^3$ increase) is higher than noted above for total mortality studies addressing multiple pollutants (100 $\mu g/m^3$ RR ≈ 1.03 to 1.05), supporting past observations that the elderly represent a population especially sensitive to health effects of air pollution.

A second recent study directly examining PM_{10}-mortality associations in the elderly was that by Ostro et al. (1996) in Santiago, Chile. For the overall population, the 100 $\mu g/m^3$ PM_{10} RR estimate was 1.08, but for the population aged 65 and greater, it rose to an estimate of RR = 1.11 in the same model specification. Thus, these directly comparable estimates (i.e., using the

same model specification and population) suggest that the elderly experience roughly a 40 percent higher excess risk from exposure to PM air pollution than the total population.

In contrast to the consistent results across the several studies described above, it should be noted that the analysis of deaths in the elderly population in France by Derriennic et al. (1989) discussed previously found no associations with TSP, whereas SO_2 was associated with total elderly deaths in both cities studied. No PM_{10} or fine particle metric was considered, however. Also, Li and Roth (1995) reported no significant association between TSP and daily deaths in the elderly in Philadelphia.

Overall, considering the historical pollution episode evidence and the results of recent PM_{10}-mortality analyses considering elderly populations, elderly adults appear to represent a population especially at risk to the mortality implications of acute exposure to air pollution, including PM.

12.3.1.4 Short-Term PM_{10} Exposure Associations with Daily Mortality in Children

As with analyses of PM-mortality associations for the elderly, few studies have directly examined PM-mortality associations in children. While the previously discussed London Fog episode yielded the greatest increased risk in the older population (e.g., the episode mortality risk versus the week before the episode increased by a factor of 2.74 for persons >45 years old), the second highest increase in risk was in the neo-natal group (ratio = 1.93 for children < 1 year) (United Kingdom Ministry of Health, 1954). More recently, as described above, Schwartz (1994c) examined increased risk of death in Philadelphia, PA for relatively high versus low TSP days during 1973 to 1980 by age, but concluded that no pattern of increased risk emerged until age 35 and above (e.g., the high/low TSP mortality ratio for < 1 year of age was 1.01). The author noted increased risk of death on high PM days for children 5 to 14 years old, which he suggested may be due to their greater time spent outdoors than other ages, though he notes that the small numbers of deaths in this age group suggest caution in such interpretations.

A recent analysis of PM_{10} pollution and mortality in Sao Paulo, Brazil provides further insight into the potential mortality effects of PM_{10} on children. Saldiva et al. (1994) studied respiratory mortality among children < 5 yrs old in Sao Paulo during May 1990 to April 1991. The environmental variables considered included PM_{10}, SO_2, NO_x, O_3, CO, temperature, and humidity. PM_{10} was not measured gravimetrically, but by beta gauge readings calibrated to

mass. Pollutants were considered in the analysis in the form of 3-day moving averages of concentration (i.e., averages of the same-day and the two prior day's concentrations). Monitoring data from multiple sites were averaged for each pollutant (e.g., 8 sites for PM_{10}). Prior to the analysis, mortality counts were adjusted using a square root transformation to address their non-normal distribution, which results in part from low daily counts (mean = 3.0 deaths/day). Season was addressed by including both seasonal and monthly dummy variables in all regressions. Weather was only crudely addressed, in that only two dummy variables for extreme temperature and two for extreme relative humidity were considered. Day-of-week effects were addressed by the inclusion of six dummy variables, but none were significant. Autocorrelation was not directly addressed in the analyses. Despite the limited data set size, a significant mortality association was found with NO_x, but not with any other pollutant. No such association was found for non-respiratory mortality, which is supportive of the interpretation of the air pollution-respiratory mortality association as causal. In the multiple pollutant model, the PM_{10} coefficient actually becomes negative (though non-significant), which is likely due to its high intercorrelation with NO_x over time ($r = 0.68$). The high interdependence between NO_x and most of the other pollutants caused the authors to note that "interplay among pollutants causing respiratory damage is very difficult to exclude". Thus, while there appeared to be an air pollution association with mortality in children, this study found the strongest association with NO_x, though the high intercorrelation among pollutants makes it difficult to designate the effects noted to any one pollutant in this case.

Overall, there is an indication among these various analyses that children could be susceptible to the mortality effects of air pollution exposure in general but it is difficult, given the limited and somewhat conflicting available results, to ascribe any such association to PM pollution in particular.

12.3.1.5 Short-Term PM_{10} Exposure Associations with Daily Mortality in Other Susceptible Subgroups

Throughout the results and discussions presented above regarding the effects of acute PM exposure on human mortality, a consistent trend was for the effect estimates to be higher for the respiratory mortality category. This lends support to the biological plausibility of a PM air pollution effect, as the breathing of toxic particles would be expected to most directly affect the respiratory tract and these results are consistent with this expectation. For example, the

respiratory mortality relative risk estimates presented in Table 12-3 are all higher than the risks for the population as a whole. Of particular interest is to compare the relative risk values for each study, which yield the most direct and appropriate comparisons as follows for: (a) the Santa Clara study (Fairley, 1990), where the respiratory mortality RR of PM was 4.3 times as large as for deaths as a whole (i.e., 3.5/0.8, in Table 12-3); (b) the Philadelphia, PA study (Schwartz and Dockery, 1992a), where the respiratory mortality RR of PM was 2.7 times as large as for death as a whole (i.e., 3.3/1.2, in Table 12-3); (c) the Utah Valley study (Pope et al., 1992), where the respiratory mortality RR of PM_{10} was 2.5 times as large as for deaths as a whole (i.e., 3.7/1.5, in Table 12-3); and (d) the Birmingham, AL study (Schwartz, 1993a), where the respiratory mortality RR of PM_{10} was 1.5 times as large as for deaths as a whole (i.e., 1.5/1.0, in Table 12-3). More recently, the Santiago, Chile PM_{10} study by Ostro et al. (1996), reported that the respiratory mortality RR of PM_{10} was 1.8 times as large as for deaths as a whole (i.e., 1.15/1.08 RR for a 100 $\mu g/m^3$). Thus, in these studies, the PM RR for respiratory diseases is indicated to range from 50% to over 400% higher for respiratory disease categories than for all causes of death, indicating that increases in respiratory deaths are a major contributor to the overall PM-mortality associations noted previously. Moreover, since evidence suggests that an acute pollution episode is most likely inducing its primary effects by stressing already compromised individuals (rather than, for example, inducing chronic respiratory disease from a single air pollution exposure episode), the above results indicate that persons with pre-existing respiratory disease represent a population especially at risk for mortality implications of acute exposures to PM-related air pollution.

12.3.1.6 Conclusions

In overall summary, the time-series mortality studies reviewed in this and past PM criteria documents provide strong evidence that ambient air pollution is associated with increases in daily human mortality. Recent studies provide confirmation that such effects occur at routine ambient levels and suggest that such effects extend below the present U.S. air quality standards. Furthermore, these new PM studies are consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. Overall, the PM_{10} relative risk estimates derived from the most recent PM_{10} total mortality studies suggest that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is associated with an effect of the order of RR = 1.025 to 1.05 in the general

population, with even higher relative risks indicated for the elderly sub-population and for those with pre-existing respiratory conditions, both of which represent sub-populations especially at risk to the mortality implications of acute exposures to air pollution, including PM.

There is relatively little information on acute mortality effects associated with fine particles ($PM_{2.5}$) and coarse particle (PM_{10} - $PM_{2.5}$) components of PM. The recent analyses by Schwartz et al. (1996) greatly extend the previous investigations of data from the Six City Study. The relationship between excess mortality and $PM_{2.5}$ is similar in magnitude in all six cities (RR from 1.026 to 1.055 per 25 $\mu g/m^3$ $PM_{2.5}$) and statistically significant in five of the six cities. The relationship between excess mortality and coarse particles is much smaller and not significant in four of these cities, negative for Topeka (where the coarse particles are predominantly of crustal origin) and statistically significant only for Steubenville (where the coarse particles are probably predominantly from industrial combustion sources), RR = 1.053 per 25 $\mu g/m^3$. The relationship between excess mortality and sulfates is somewhat weaker than for $PM_{2.5}$, but still statistically significant. The relationship with aerosol acidity is even smaller, and not statistically significant. It is also not clear whether the large and statistically significant effects of fine particles on mortality should be attributed to the sulfate fraction of $PM_{2.5}$, or whether there is similar risk associated with the non-sulfate components. It is not clear whether to attribute the predictiveness of sulfates to the fact that sulfates are fine particles, or to some other property such as their acidity, even though aerosol acidity may not have been as adequately characterized in the Six City Study. This is because the data base is so much smaller than for sulfates and particles as H^+ was monitored on only 18% as many days as PM_{10} and $PM_{2.5}$. Even when monitored, H^+ was below the detection limit on many days, which further limited the data set. Finally, these analyses show that while coarse particles appear to play a much smaller role in acute mortality than fine particles, there may be at least some situations (such as in Steubenville) where coarse fraction particles cannot be entirely ruled out as possibly contributing to excess mortality along with fine particles.

12.3.2 Morbidity Effects of Short-Term Particulate Matter Exposure

12.3.2.1 Hospitalization and Emergency Visit Studies

Introduction to Hospitalization Studies

Hospitalization for a respiratory illness diagnosis can provide a measure of the respiratory morbidity status of a community during a specified time frame. Such respiratory diagnoses include hospitalization for pneumonia, influenza, and asthma. Various factors affect the epidemiology of admissions for these diagnosis. Factors shown to be independently associated with respiratory hospitalization include poor socioeconomic level, type of heating, and exposure to second-hand tobacco smoke (Thomson and Philion, 1991).

Beard et al. (1992) evaluated interobserver variability during data collection for a population based study of asthma using medical record information. The results suggested that data collection was carried out reliably in this study. Osborne et al. (1992) evaluated the diagnosis of asthma in 320 inpatient and outpatient records bearing the diagnosis of asthma for the period 1970 through 1973 and 1980 through 1983 in a health maintenance organization (HMO). The majority of charts examined exhibited a clinical picture consistent with asthma. The increases in "definite asthma" among outpatients from the 1970s to the 1980s reflected increasing chart documentation among physicians. Jollis et al. (1993) study of hospital insurance claim information to include medicare indicated that insurance claim data lack important diagnostic and pragmatic information when compared with concurrently collected clinical data in the study of ischemic heart disease as an example.

Wennberg et al. (1984) found that hospital admissions for the following diagnosis- related groups showed a very high variation by hospital market area: pediatric pneumonia, pediatric bronchitis and asthma, chronic obstructive lung disease, and adult bronchitis and asthma. Richardson et al. (1991) found that adjusted admission rates for respiratory distress (COPD, asthma, bronchitis, and pneumonia) varied up to 3.09-fold between the highest and lowest hospital market areas in 1986 for the state of Ohio. The reasons for differences between hospital market areas are found in the incidence of illness, variability of local resources, access to care, practice styles of area physicians, numbers of physicians and pulmonologists, inconsistencies in diagnoses, conflicting treatment methodologies, lack of consensus of care, quality of outpatient care, and varying criteria for admission among principal variables. For example, Wennberg et al. (1984) documented great geographic variability in hospital admission rates for adult community acquired pneumonia. This variation suggests that physicians do not use consistent criteria for hospitalization. Specific indications for admission do exist such as the Appropriateness Evaluation Protocol (AEP). Substitution of outpatient for inpatient care is a

major strategy promoted to reduce health care cost and as such the majority of patients with community acquired pneumonia are treated as outpatients.

Fedson et al. (1992) state that vaccination practices may play a role in hospitalization rates for influenza and associated respiratory disorders. Despite public health recommendations for influenza vaccination for elderly persons, the vaccine has not been widely used, in the United States only 32% of elderly persons may be vaccinated each year. During the influenza outbreak period most persons with respiratory conditions requiring hospitalization (92%) resided in private residence rather than in nursing homes. Also while previous epidemiologic studies arbitrarily defined outbreak periods as the first three months of the year this study indicated that hospitalization discharges for influenza mainly occurred during the period December 1 through February 28.

The number and rate of patients discharged by age and first-listed diagnosis in the United States in 1991 are shown in Table 12-6 for all conditions, respiratory disease, heart and circulatory diseases and neoplasma. Disease of the respiratory system represent approximately 10% of all conditions. The number and rate for pneumonia of the respiratory diseases listed in Table 12-6 are highest for all ages primarily due to the high number and rate for 65 years and over. Specific diseases of the respiratory system are shown in Table 12-7 for 1992, in which five groupings predominate. "Pneumonia organism unspecified" is the largest group.

TABLE 12-6. NUMBER AND RATE OF PATIENTS DISCHARGED FROM SHORT-STAY HOSPITALS, BY AGE AND FIRST-LISTED DIAGNOSIS: UNITED STATES, 1991[a]

First-listed diagnosis	ICD-9-CD code	All ages	Under 15 years	15-44 years	45-64 years	65 years and over	All ages	Under 15 years	15-44 years	45-64 years	65 years and over
		Number of patients discharged in thousands					Rate of patients discharged per 10,000 population				
All conditions		31,098	2,498	11,620	6,173	10,806	1,241.1	453.2	993.4	1,321.6	3,403.1
Diseases of the respiratory system	460-519	3,052	736	500	530	1,286	121.8	133.6	42.7	113.4	405.2
Acute respiratory infections	460-466	518	220	68	75	156	20.7	39.8	5.8	16.0	49.2
Pneumonia	480-486	1,088	214	133	152	589	43.4	38.9	11.4	32.5	185.5
Asthma	493	490	187	128	85	90	19.6	33.9	10.9	18.2	28.5
Diseases of the circulatory system including heart disease	390-459	5,338	28	396	1,509	3,405	213.1	5.1	33.9	323.1	1,072.4
Neoplasms	140-239	2,001	52	363	626	960	79.9	9.5	31.0	133.9	302.3

[a]Discharges from non-Federal hospitals. Excludes newborn infants. Diagnostic groupings and code number inclusions are based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CD).

Adapted from National Center for Health Statistics (1993b).

TABLE 12-7. NUMBER OF FIRST-LISTED DIAGNOSES FOR INPATIENTS DISCHARGED FROM SHORT-STAY NON-FEDERAL HOSPITALS, BY ICD-9-CM CODE, AGE OF PATIENT, AND GEOGRAPHIC REGION OF HOSPITAL: UNITED STATES, 1992

First-listed diagnosis	ICD-9-CM code	Total	Age				Region			
			Under 15 years	15-44 years	45-64 years	65 years and over	Northeast	Midwest	South	West
		Number of first-listed diagnoses in thousands								
Diseases of the respiratory system	460-519	2,923	735	460	501	1,227	635	704	1,139	445
Acute Bronchitis	466	251	149	21	23	58	49	64	104	33
Viral Pneumonia	480	39	27	*	*	*	*	12	12	10
Pnuemoccal pneumonia	481	53	6	10	10	27	10	14	17	12
Other bacterial pneumonia	482	202	11	26	31	134	34	47	87	35
Pneumonia, other specified organisms	483	20	*	*	*	8	*	5	8	*
Broncho pneumonia, organism unspecified	485	45	16	*	*	22	9	9	22	5
Pneumonia, organism unspecified	486	700	145	87	108	360	134	177	287	101
Influenza	487	13	*	*	*	6	*	*	*	*
Bronchitis, unspecified	490	23	9	*	6	*	*	*	11	*
Chronic Bronchitis	491	201	*	7	52	141	45	40	86	30
Emphysema	492	29	--	*	8	18	6	8	12	*
Asthma	493	463	193	117	78	76	116	113	152	83

*Figure does not meet standard of reliability or precision.
Adapted from National Center for Health Statistics (1994b).

In the last decade, large increases have occurred in asthma hospitalization rates among the pediatric population. While this pattern has been seen in all age, race and gender groups the most severely affected group is urban black children (Gerstman et al., 1993). This increase was largest among 0 to 4 years old with blacks having approximately 1.8 times the increase of whites (Gergen and Weiss, 1990). During this time, total hospitalization decreased while admissions for lower respiratory tract disease also had a slight decrease (Gergen and Weiss, 1990).

There are differences in the frequency of admission for asthma by age and gender (Skobeloff et al., 1992). Asthma morbidity is known to exhibit seasonal periodicity. For persons ages 5 through 34 years, hospitalization peaked in September through November whereas mortality trends peaked in June through August. For individuals 65-years-old or older, both asthma hospitalization and mortality demonstrated increases during December through February (Weiss, 1990). Crane et al. (1992) states that the most valid and reliable marker of asthma readmission is the number of hospitalization admissions for asthma in the previous 12 mo. In New York City, Carr et al. (1992) found large geographic variations for asthma hospitalization with the highest rate concentrated in the city's poorest neighborhoods. The patients are heavily dependent on hospital outpatient departments and emergency rooms for their ambulatory care. Differences in medical practice styles, reflecting the exercise of physicians discretion in the way illnesses are treated, are important determinants of temporal variation and geographic variation in hospital utilization for many medical conditions.

Storr and Lenney (1989) observed a long term variation in children's hospitalization for asthma and school holidays. The admission rate fell during holidays and there were two or more peaks during terms. The pattern is consistent with a largely viral etiology for asthmatic attacks throughout the year. They postulated that school holidays disrupt the spread of viral infectious in a community, with synchronization of subsequent attacks. Travel during holidays may facilitate acquisition of new viral strains by the community.

Based on a total of 450,000 hospitalizations for asthma and an estimated U.S. population of 10,000,000 asthmatics, the incidence of hospitalization for all asthmatic subjects is about 45 per 1,000 asthmatics (National Institutes of Health, 1991).

Hospital Admission Studies

This section discusses studies of hospital admissions, outpatient visits and emergency room visits, both within the United States and from countries with different medical care systems which may have different medical care practices. Most PM-hospitalization studies consider at least two different classes of admissions. Thus, results of such studies are summarized by class in Tables 12-8 through 12-11.

Bates and Sizto (1983, 1986, 1987) reported results of a study relating hospital admissions in southern Ontario to air pollution levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1985 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and $S0_2$ or COHs in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory admissions (both asthma and nonasthma) in summer and sulfates and ozone, but not to summer COH levels. However, Bates and Sizto note that the data analyses are now complicated by long-term trends in respiratory disease admissions unlikely related to air pollution, but they nevertheless hypothesize that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer but not in the winter. In a more recent paper, Bates and Sitzo (1987) extend the time period through 1983 and include additional air sampling data not available previously. The monitoring was from 17 air sampling stations and included O_3, sulfate fraction, SO_2, NO_2, and COH. Stepwise multiple regressions confirmed the earlier findings that there was a consistent summer relationship between sulfates and O_3 with hospital admissions. The analyses did not adjust for time trends, trends within the summer season, or serial correlation.

Lipfert and Hammerstrom (1992) conducted a 6-year study of hospital admissions in southern Ontario for 1979 to 1985. Daily hospital admissions were obtained from the Ontario Ministry of Health, the same data base used by Bates and Sitzo (1983, 1986, 1987). The primary focus of the study was on respiratory illness in one of the following ICD codes: 466 acute bronchitis, 480 to 482 or 485 pneumonia, 490 to 492 chronic bronchitis, emphysema, or 493 asthma. Three regions were defined with slightly different air pollution exposures, based on data from the Ontario Ministry of the Environment for SO_2, NO_2, O_3, sulfate fraction, COH, and TSP. Some stations monitored every three or six days and

TABLE 12-8. HOSPITAL ADMISSIONS AND OUTPATIENT VISIT STUDIES FOR RESPIRATORY DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Burnett et al. (1994) All ages in Ontario, Canada, 1983-1988	9 monitoring stations measuring sulfate	sulfate means ranged from 3.1 to 8.2 μg/m^3	108	Lin. regress. on filtered data, 1-d lag best	Ozone	Temperature	none	1.03 (1.02, 1.04)
Thurston et al. (1994a,b) All ages in Ontario, Canada, July and August, 1986-1988	3 monitoring stations measuring sulfate, TSP, and PM_{10}	mean sulfate ranged 38 to 124 (nmole/m^3), PM_{10} 30 to 39 μg/m^3, TSP 62 to 87 μg/m^3	14.4	Linear regression on filtered data, 0-d lag best	Ozone, H+, SO_2, NO_2	Temperature	none ozone	PM_{10} 1.23 (1.02, 1.43) PM_{10} 1.12 (0.88, 1.36)
Thurston et al. (1992) All ages in Buffalo, Albany, New York City, July and August, 1988-1989	3 monitoring stations (one per city) measuring sulfate, H+	(values not given)	Buffalo, 24 Albany, 12, New York, 137	Linear regression on filtered data	Ozone, H+	Temperature	ozone	(not given for PM measures)
Schwartz (1995a) Elderly in New Haven, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 41, 10% tile = 19, 90% tile = 67	8.1	Poisson log-linear regression, 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 29; 10% tile = 16; 90% tile = 45; SO_2 (ppb): mean = 30; 10% tile = 9; 90% tile = 61	Temperature and dew point adjusted for in the moving average	none SO_2 (2 day lag)	1.06 (1.00, 1.13) 1.07 (1.01, 1.14)
Schwartz (1995a) Elderly in Tacoma, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 37, 10% tile = 14, 90% tile = 67	4.2	Poisson log-lin. regress. 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 25; 10% tile = 13; 90% tile = 36; SO_2 (ppb): mean = 17; 10% tile = 6; 90% tile = 28	Temperature and dew point adjusted for in the moving average	none SO_2 (2 day lag)	1.10 (1.03, 1.17) 1.11 (1.02, 1.20)

TABLE 12-8 (cont'd). HOSPITAL ADMISSIONS AND OUTPATIENT VISIT STUDIES FOR RESPIRATORY DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz et al. (1996) Elderly in Cleveland, OH	PM_{10}, O_3, No of sites not given	mean = 43 $\mu g/m^3$	2.2	Generalized additive Poisson model	O_3	temperature, dew point	none	1.06 (1.00, 1.11)
Schwartz (1996) Elderly (≥65) in Spokane, WA	PM_{10}, O_3, No. of sites not given	mean = 46 $\mu g/m^3$	3.9	Generalized additive Poisson model	O_3	temperature, dew point	none	1.08 (1.04 to 1.14)
Schwartz et al. (1993) Asthma visits, <65 age, Seattle, WA	PM_{10} 1 site	mean = 29.6 $\mu g/m^3$ min = 6 max = 103 $\mu g/m^3$	7.1 Asthma	Poisson regression model	SO_2, O_3	temperature	none	1.12 (1.04, 1.2) per 30 $\mu g/m^3$ PM_{10}
Hefflin et al. (1994) Emergency room visits, All ages	PM_{10} 1 site	mean = 40 $\mu g/m^3$ min = 3 max = 1,689 $\mu g/m^3$	13.7 Bronchitis	Poisson regression model (GEE)	None	temperature	none	3.5% per 100 $\mu g/m^3$ PM_{10}
Gordian et al. (1996) Outpatient visits for asthma	PM_{10} 1 site	mean = 45.54 $\mu g/m^3$ min = 5 max = 565 $\mu g/m^3$	2.12 Asthma	Poisson multiple regression model	CO	temperature	CO	2.5% ↑ per 10 $\mu g/m^3$ PM_{10}

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

TABLE 12-9. HOSPITAL ADMISSIONS STUDIES FOR COPD

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Sunyer et al. (1993) Adults in Barcelona, 1985-1989	15 monitoring stations measuring black smoke	winter 33% tile = 49, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	12	Autoregressive linear regression analysis, 0-d lag best	Sulfur dioxide, winter 33% tile = 49 $\mu g/m^3$, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	min temp, dummies for day of week and year	none SO_2	winter: 1.15 (1.09, 1.21) summer: 1.05 (0.98, 1.12) winter: 1.05 (1.01, 1.09) summer: 1.01 (0.97, 1.05)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19 90% tile - 77	2.2	Autoregressive Poisson model, 0-d lag best	Ozone, mean = 25 ppb, 10% tile = 14, 90% tile = 37	7 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.13 (1.04, 1.22)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10% 2.2 tile = 18, 90% tile = 58	2.2	Autoregressive Poisson model, 1-d lag best	Ozone, mean = 26 ppb, 10% tile = 11, 90% tile = 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.25 (1.10, 1.44)
Schwartz (1996) Elderly (>65) in Spokane, WA	No of sites not given, PM_{10}, O_3	mean = 46 $\mu g/m^3$	3.9	Generalized additive Poisson model	O_3	temperature, dew point	none	1.17 (1.08, 1.27)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} mon. stations, data for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	15.7	Poisson auto-regress. mod. using GEE, 0-d lag best	Ozone: mean 21 ppb; 10% tile 7: 90% tile 36	Dummy variables ozone for temp, month, lin. & quad. time trend	none	1.10 (1.02, 1.17)

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

TABLE 12-10. HOSPITAL ADMISSIONS STUDIES FOR PNEUMONIA

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10% tile = 18, 90% tile = 58	6.0	Autoregressive Poisson mod., 1-d lag best	Ozone, mean 26 ppb; 10% tile 11; 90% tile 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.08 (1.01, 1.15)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19, 90% tile = 77	5.9	Autoregressive Poisson modl, 0-d lab best	Ozone, mean 25 ppb; 10% tile 14; 90% tile 37	7 cat. of temp. & none dew pt., month, year, lin. & quad. time trend	none	1.09 (1.03, 1.15)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} mon. stations, data for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	15.7	Poisson autoregress. mod. using GEE, 0-d lag best	Ozone, mean 21 ppb; 10% tile 7; 90% tile 36	Dummy variables ozone for temp, month, lin. & quad. time trend	ozone	1.06 (1.02, 1.10)
Schwartz (1996) Elderly ($\geq$65) in Spokane, WA	PM_{10}, O_3, No. sites not given	mean = 46 $\mu g/m_3$	3.9	Generalized additive Poisson model	Ozone	temperature, dew point	none	1.06 (0.98, 1.13)
Schwartz (1994g) Elderly in Philadelphia	No. of sites not given TSP, O_3, SO_2	not given	not given	Generalized additive Poisson model	Ozone, SO_2	temperature, dew point	none	1.22 (1.10, 1.36)

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

TABLE 12-11. HOSPITAL ADMISSIONS STUDIES FOR HEART DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz and Morris (1995) Elderly in Detroit 1986-1989 Ischemic Heart Disease	2 to 11 PM_{10} monitoring stations, data available for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	44.1	Poisson auto-regressive model using GEE, 0-d lag best	SO_2, mean = 25 ppb, 10% tile = 11, 90% tile = 44 CO, mean 2.4 ppm, 10% tile 1.2, 90% tile = 3.8	Dummy vars. for temp, month, lin. & quad. time trend	none	1.018 (1.005, 1.032)
							ozone, CO, SO_2	1.016 (1.002, 1.030)
Burnett et al. (1995) All ages in Ontario, Canada, 1983-1988 Cardiac disease admission	22 sulfate monitoring stations	station means ranged from 3.0 to 7.7 in the summer and 2.0 and 4.7 in the winter	14.4	Linear regression on a 19 day linear filter, 1-d lag best	Ozone averaged 36 ppb	Temperature included in separate analyses by summer and winter	none	1.03 (1.02, 1.04)
							ozone	1.03 (1.02, 1.05)

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

averages were taken by region for those monitors present. A Box-Jenkins ARIMA multiple regression model was used to analyze the data. Bivariate correlations were calculated between the pollutants and respiratory illness. Stepwise multiple regressions did not include TSP as a significant factor, but O_3 was significant for January and February and SO_2 was significant for some regions in July and August.

Burnett et al. (1994) studied hospital admissions in southern Ontario, using a broader area than that used by Bates and Sitzo (1983, 1986, 1987). The respiratory admissions were for 1983 to 1988 and were restricted to the ICD9 codes of 466, 480 to 486, 490 to 494, and 496. The non respiratory control admissions included the codes of 280 to 281.9, 345 to 347, 350 to 356, 358 to 359.5, 530 to 534, 540 to 543, 560 to 569, 571, 572, 574 to 578, 594, and 600. Twenty-two monitoring stations were used to estimate daily O_3 and sulfate fraction data; meteorological data came from 10 different stations. The daily fluctuations in admissions were related to the pollution and meteorological data after subtracting a 19 term linear trend as discussed by Shumway et al. (1983). The rates were analyzed using a random effects model, where hospitals were assumed to be random. The estimates were obtained using the generalized estimating equations (GEE) of Liang and Zeger (1986). In general, O_3, sulfate fraction, and temperature were all predictors of hospital admissions; but O_3 tended to be more significant than did sulfate fraction. The models predicted about a 3% increase in respiratory hospital admissions for about a 14 $\mu g/m^3$ concentration of sulfate fraction.

Thurston et al. (1994b) studied hospital admissions in the Toronto metropolitan area. during the months of July and August of 1986, 1987, 1988 and restricted to the following causes: total respiratory (ICD9 codes 466, 480, 481, 482, 485, 490 to 493), asthma (493), and non respiratory control (365, 430, 431, 432, 434, 435, 531, 543, 553.3, 537, 540, 541, 542, 543, 590). There were no stated restrictions on age. Pollution data consisted of acidity (H^+) and sulfate data measured at three sites during the three summer seasons. In addition, O_3, NO_2, and SO_2 and daily 24-h $PM_{2.5}$ and PM_{10} were measured at several other stations. Meteorological measurements were available from two of the monitoring sites. Ordinary least squares analyses were calculated after the environmental variables were detrended. The data for the three summers were combined. In general, O_3 was the strongest predictor of hospital admissions above the strong effect of temperature. There was some suggestion of an effect from PM_{10},

especially for total respiratory admissions. There were strong associations with H^+ and with $SO_4^=$. Non-linear temperature terms were not fitted.

Sunyer et al. (1991, 1993) studied daily emergency room admissions for COPD in adults in Barcelona, Spain. The original study included admissions for the years 1985 and 1986. A specially trained physician collected data from clinical records from the four largest hospitals in Barcelona. A panel of chest physicians defined expressions used to determine the diagnosis of COPD. Seventeen manual samplers and two automatic samplers took 24-h measurements of SO_2, black smoke, CO and O_3. Neither SO_2 nor black smoke exceeded the European Community standards. A Box-Jenkins ARIMA (auto-regressive integrated moving average) time series model was used to analyze the results. COPD was found to be related to SO_2, black smoke, and CO. The relationship with black smoke was especially pronounced for temperatures greater than 11.7° C. In the later paper, Sunyer et al. (1993) included the larger time period of 1985 to 1989. The study was restricted to individuals in the four largest hospitals at least 14 years of age. Fifteen manual samplers provided SO_2 and black smoke measurements. Ridge regression (a modification of standard multiple linear regression) was used to analyze the daily admissions, but the analyses were done separately by season. Ridge regression is a conservative method of handling collinear variables, but it does not take into account the effects of non-normality of counts. Lag variables to adjust for the autocorrelation were selected according to the methodology of Box and Jenkins (1976). Significant changes in admissions were found for both SO_2 and black smoke for the winter season, but only SO_2 was significant in the summer.

Hospital admissions for all hospitals in the Birmingham, AL, SMSA were studied by Schwartz (1994e). The admissions were restricted to pneumonia (ICD-9 codes 480 to 487) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490 to 496) from January 1, 1986 to December 31, 1989. Only persons age 65 were included in the analysis. Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Birmingham stations reporting on a given day. The author used three different models for the analysis including (1) Fourier series adjustments for season with linear and quadratic terms for temperature, dew point, and time trend, (2) a similar model with cubic splines used instead of Fourier series, and (3) a nonparametric approach. Serial correlation was adjusted for using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The relative risk of pneumonia was found to be about 1.16 (1.05 to 1.28) corresponding to an

increase of 100 $\mu g/m^3$ of PM_{10}. The relative risk of COPD was found to be about 1.24 (1.05 to 1.45) for an increase of 100 $\mu g/m^3$ of PM_{10}. Associations with O_3 were found to be slightly weaker.

Schwartz (1994d) also studied hospital admissions for the elderly in Detroit, restricted to pneumonia (ICD-9 codes 480 to 486) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490 to 496) from January 1, 1986 to December 31, 1989. Only persons age 65 or older were included in the analysis. Separate counts were constructed for asthma (493) and all other COPD (491 to 492 and 494 to 496). Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Detroit metropolitan area stations reporting on a given day. The author used three different approaches to the analysis, including a nonparametric approach. Serial correlation was adjusted for using autoregressive terms which were estimated using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The estimated relative risk coefficient for pneumonia was 1.012 (1.004 to 1.019) for an increase of 10 $\mu g/m^3$ of PM_{10}. The estimated relative risk for COPD was 1.020 (1.004 to 1.032) for an increase of 10 $\mu g/m^3$ of PM_{10}. Associations with O_3 were also found, but the dose response relationship was not as consistent.

Hospital admissions for all hospitals in Spokane, WA, were also studied by Schwartz (1996). The admissions were restricted to respiratory disease (ICD-9 codes 460 to 519) from January 1, 1988 to December 31, 1990. Only individuals $\geq$ 65 yrs were included in the analysis. Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Spokane stations reporting on a given day. PM_{10} values averaged 46 $\mu g/m^3$ with 10 and 90 percentile values of 16 and 83 $\mu g/m^3$. Monitoring for SO_2 in Spokane from January to April 1985 yielded an average SO_2 concentration of 0.0037 ppm. The author used three different models for the analysis, including (1) Fourier series adjustments for season with linear and quadratic terms for temperature, dew point, and time trend, (2) a similar model with cubic splines used instead of Fourier series, and (3) a nonparametric approach. Serial correlation was adjusted for using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The relative risk of respiratory disease was about 1.08 (1.04 to 1.14) corresponding to an increase of 50 $\mu g/m^3$ of PM_{10}. Associations were also found with O_3, giving a relative risk of 1.24 (1.00 to 1.54) for an increase of 50 $\mu g/m^3$. Inclusion of both pollutants in the model had little effect on either estimate.

Pönkä and Virtanen (1994) studied hospital admissions for exacerbations of chronic bronchitis (ICD-9 code 491) and emphysema (ICD-9 code 492) in Helsinki, Finland during 1987 to 1989. Individuals with the diagnosis of asthma (ICD9 code 493) were excluded. Sulfur dioxide was measured hourly at four stations, NO_2 at two stations, and O_3 at one station; TSP was measured every other day at four stations and every third day at two stations. Meteorological information was available from a single station but the location was not specified. Daily admissions were analyzed using Poisson regression as described by McCullagh and Nelder (1989). The model included variables for season, day of week, year, and influenza epidemics. The authors report that the day of week variables effectively reduced the autocorrelation, and so autocorrelation terms were not included due to their difficulty of interpretation. For persons <65 years old, the only effects seen were with SO_2 on the same day or three days previous. For individuals older than age 64, the only effect seen was for NO_2 six days previous. Although these results are difficult to interpret, the study did not find any results suggesting a PM effect.

Pönkä (1991) also studied hospital admissions for asthma (ICD9 code 493) in Helsinki during 1987 to 1989. Persons with the diagnosis of bronchiolitis were excluded. Sulfur dioxide was measured hourly at four stations, NO_2 at two and O_3 at one; TSP was measured every other day at four stations and every third day at two. Meteorological information was available from a single station. The analysis was done using simple and partial age specific correlations of asthma admissions with mean daily concentrations of SO_2, NO_2, NO, CO, TSP, O_3, temperature, wind speed and humidity. No adjustment was made for season or serial correlation. TSP was found to be significantly correlated with hospital admissions, but was less correlated than some of the other pollutants.

White et al. (1994) studied asthma outpatient clinic visits of children at Grady Memorial Hospital in Atlanta. The encounter forms for each child between June 1, 1990 and August 31, 1990 were abstracted, excluding visits when pneumonia or bronchiolitis was mentioned. Hourly O_3 measurements were available from two stations in the area. PM_{10} data were available from the middle of July, but data before that time had to be estimated using visibility data from Hartsfield International Airport. Clinic visits were increased when O_3 exceeded 0.11 ppm. Using a Poisson regression model, the estimated increase, as measured by a rate ratio, was 1.02 (CI = 0.96, 1.13) for a 10 $\mu g/m^3$ increase in PM_{10}.

Tseng et al. (1992) studied quarterly hospital discharges for asthma (ICD-9 Code 493) from the computerized hospital inpatient data base of the Medical and Health Department of Hong Kong. The study ran from the second quarter of 1983 to the last quarter of 1989. The discharges were split into four groups: under age 1, age 1 to 4, age 5 to 14, and adult. Quarterly averages of SO_2, NO_2, O_3, TSP and RSP values were obtained from the environmental protection unit of the Hong Kong Government. Multiple regression analyses were performed on the hospitalization rates using the four different age groups as the dependent variables and the pollution values as the independent values. Season and year were used as covariates, but no meteorological variables were included in the analyses. The significant correlations were between TSP and hospitalization rates for children aged 1 to 4 and children aged 5 to 14. The correlations for RSP tended to be similar, but smaller in magnitude.

Asthmatic admissions and emergency room visits to the Pediatric Department of the Hospital de S. Joäo (serving the Oporto area of Portugal) during the period from 1983 to 1987 were studied by Queirós et al. (1990). Air pollution was estimated from measurements of SO_2 and black smoke (BS) taken daily at four stations. The admissions were adjusted so that the values represented deviations from the average for a particular month or year. No correlation was found between daily, monthly, or quarterly mean admissions or visits and BS levels but SO_2 levels were correlated with monthly mean admissions. The authors concluded that there was no evidence for PM pollution effects on admissions or visits.

During January 1985, large parts of Europe from western Germany to Great Britain experienced a pollution event traced to emission sources in Central Europe. This event was tracked by monitoring stations in several countries as it moved from east to west, and then finally dissipated over the North Sea. Very high levels of PM, SO_2, and NO_x were reported. Wichmann et al. (1989) studied mortality, hospital admissions, ambulance transports and outpatient visits for respiratory and cardiovascular disease in West Germany during the 1985 event. During that time, daily suspended particulate matter reached 600 μg/m, SO_2 reached 830 $\mu g/m^3$, and NO_2 reached 410 $\mu g/m^3$. Total mortality rose immediately with the increase in pollution (January 16, 1985), and reached a maximum on January 18. The increase in mortality was about 8 percent. Similarly, increases in hospital admissions (15 percent), outpatient visits (12 percent), and ambulance transports (28 percent) were seen. Wichmann et al. (1988a,b)

reported on other events in 1986 and 1987 which related lung function changes to SO_2 levels but did not report PM data.

Walters et al. (1994) studied hospital admissions in Birmingham, England. The admissions were restricted to asthma or acute respiratory disease (ICD9 codes of 466, 480 to 486, and 490 to 496) for the period of April 1988 to March 1990. No age restrictions were indicated. Seven monitoring stations were used to estimate BS and SO_2 levels. Meteorological information came from the University of Birmingham Department of Geography. The data were divided into four seasons for analysis to control for seasonal variation in all variables. Stepwise multiple regression models were fitted to the hospital admissions data using pollution and meteorological variables as independent variables. Marginally significant regression coefficients were found for both pollutants for both endpoints, especially in the winter season. Additional analyses were run using 2-day lags of the pollution variables, and some of these were marginally significant. This study adds little to the effect of particulate matter on respiratory hospital admissions because of the difficulties in comparing black smoke to particulate fractions.

In another study, Schwartz et al. (1993), emergency room visits for 8 hospitals in the greater Seattle area were abstracted for the period September 1, 1989 to September 30, 1990. Asthma was defined as a diagnosis of ICD9 Codes 493, 493.01, 493.10, 493.90 and 493.91. Sulfur dioxide was measured at an industrial site, PM_{10} was available from a residential area north of town, and O_3 was measured at a site 20 km east of town. Poisson regression as described by McCullagh and Nelder (1983) was used to estimate the effect of pollution on asthma visits with adjustments for serial correlation using the method of Zeger and Liang (1986). Logistic regression coefficient estimated from the Poisson regression gave a values of .0036 (.0012) for PM_{10}. The pollution monitors were located far from the study population, but the analyses of partial data suggested that the station produced estimates that were highly correlated with the local data.

Urgent hospital admissions for respiratory illnesses in Montreal, Canada were collected from 14 hospitals from 1984 to 1988, and were split into asthma and non-asthma admissions (Delfino et al., 1994a,b). The definitions were similar to those used by Bates and Sitzo (1987). City-wide averages of O_3, PM_{10}, and sulfate fraction were calculated from seven selected monitoring stations. PM_{10} was measured every sixth day, and values for the other five days were estimated. A high-pass filter was used to eliminate yearly seasonal trends (see Shumway et al.,

1983). Weather variables included temperature and humidity. Regression analyses with and without autoregressive terms found few significant relationships between the health endpoints and the various pollutants.

Duclos et al. (1990) studied hospital admissions for respiratory and non-respiratory conditions during several forest fires in northern California. The fires commenced on August 30, 1987, and TSP levels increase to about 300 $\mu g/m^3$ from a background level generally below 100 $\mu g/m^3$. The analysis consisted of comparing observed versus expected rates without adjustment for serial correlation or other factors. Although there was a significant increase in visits for respiratory conditions, the same pattern appeared for visits for injuries.

Pope (1991, 1989) studied hospital admissions in the Salt Lake Basin during the period surrounding the shut-down or strike of the steel mill. According to Pope (1991), PM_{10} pollution in the Utah Valley came from many sources, but the primary source was a 45-year-old integrated steel mill with coke ovens, blast furnaces, open hearth furnaces, and a sintering plant. When in operation, the mill emitted 82 to 92% of the valley's industrial PM_{10} pollution and 50 to 70% of the total Utah Valley PM_{10} emissions. The steel mill shut down from August 1, 1986 to September 1, 1987. Winter PM_{10} levels were approximately twice as high when the mill was open compared to when it was closed. Three mountain areas of central and north central Utah were monitored for admissions to three local hospitals. Daily admissions for asthma, bronchitis, and pneumonia were recorded. PM_{10}, SO_2, and NO_2 levels were monitored at a site 5 km northeast of the steel mill. Admissions for bronchitis and asthma were higher during periods of operation of the steel mill when compared to other areas of Utah. Logistic regressions were generally not significant, but respiratory hospital admissions were associated with monthly mean PM_{10} levels.

Lamm et al. (1994) reanalyzed the data of Pope (1991, 1989). This new analysis attempted to investigate a possible viral cause of the illnesses. Monthly respiratory syncytial virus (RSV) activity was measured in terms of total monthly bronchiolitis admissions in all IHC hospitals in Utah and Salt Lake counties. Section 12.3.2.2 provides some background on RSV and childhood respiratory illness. When this variable measured as described (total monthly bronchiolitis), was included in the analysis, the significance of the effect of PM was eliminated.

Hefflin et al. (1994) compared the number of emergency room visits in southeast Washington state for twelve respiratory disorders for each day of 1991 with daily PM_{10} levels.

During two dust storms on October 16 and 21, 1991 PM_{10} reached 1,689 and 1,035 $\mu g/m^3$, respectively. Other pollutants were not measured. Airborne particles in rural eastern Washington, which are mainly volcanic in origin, fall mostly in the PM_{10} fraction and belong to the plagioclase (glass) mineral class of aluminum silicates and other oxides. The authors used a Poisson regression model to predict daily emergency room visits as a function of season, relative humidity, and one and 2-day lags of PM_{10} pollution. Variances were estimated using the generalized estimating equations with an exchangeable correlation structure as described by Liang and Zeger (1986). Daily emergency room totals for each disorder, except respiratory allergy, had a statistically significant inverse correlation with mean daily temperature. The maximum observed/ expected ratio for respiratory disorders from the dust storms on October 16 and 21 was 1.2. The author considered this relatively low ratio for such high pollution days as indicating that the high PM_{10} levels probably had a minimal public health impact. A statistically significant relationship between a year of daily PM_{10} levels for emergency room visits for bronchitis and sinusitis was found, although the estimated regression coefficient indicated a small effect. Ten other disorders, including asthma, pneumonic influenza, and COPD did not show this relationship.

Gordian et al. (1995, 1996) examined associations between daily PM_{10}, temperature measurements and daily outpatient visits for respiratory disease including asthma, bronchitis and upper respiratory conditions. The study was done in Anchorage, Alaska, where there was no industrial source of air pollution, so that PM_{10} contains primarily earth crustal material and volcanic ash. Outpatient visits were obtained from insurance claims for state and municipal cmployees and their dependents covered by Aetna insurance during the time period May 1, 1992 to March 1, 1994. The numbers of visits were modeled using a weighted 19-day moving average filter (see Kinney and Ozkaynak, 1991) to adjust for long term cycles including season. The results showed that an increase of 10 $\mu g/m^3$ in PM_{10} results in a 2.5% increase in asthma visits and a 1.2% increase in visits for upper respiratory illness. PM_{10} levels ranged from 5 to 565 $\mu g/m^3$ with a mean of 46 $\mu g/m^3$.

Thurston et al. (1992) studied hospital admissions for respiratory disease among all ages in Buffalo, Albany, and New York City during July and August, 1988-1989. Three monitoring stations (one per city) measured sulfate, H+, and ozone. A linear regression analysis on filtered

data showed relative risk of 1.05 (1.01, 1.10) for sulfate. Positive results for H^+ are discussed in detail in Section 12.5.

Schwartz (1994f) studied hospital admissions for elderly patients in Minneapolis during 1986 to 1989. Exposure measurements were obtained from 6 monitoring stations which measured PM_{10} and O_3. The mean PM_{10} value was 36 $\mu g/m^3$, the 10th percentile was 18 and the 90th was 58. The mean O_3 value was 26 ppb, the 10th percentile was 11 and the 90th was 41. An autoregressive Poisson model with 8 categories of temperature and dew point, month, year, linear and quadratic time trend was used to analyze the data. The estimated relative risk for a 100 $\mu g/m^3$ increase in PM_{10} was 1.57 (1.20, 2.06) for COPD (ICD9 490 to 496) and 1.17 (1.02, 1.33) for pneumonia (ICD9-480 to 487).

Schwartz (1994g) studied hospital admissions for pneumonia for individuals age 65 or older in Philadelphia, PA. Daily pollution estimates of TSP, SO_2, and O_3 were computed by averaging all Philadelphia stations reporting on a given day. The author used a generalized additive Poisson model including Fourier series adjustments for season, linear and quadratic terms for temperature, dew point, and time trend. The relative risk of pneumonia was found to be about 1.22 (1.10 to 1.36) corresponding to an increase of 100 $\mu g/m^3$ of TSP. Associations with SO_2 and O_3 were also significant.

Schwartz et al. (1996b) studied hospital admissions for all respiratory disease for individuals age 65 or older in Cleveland, OH. Daily pollution estimates of PM_{10} and ozone were computed by averaging all Cleveland stations reporting on a given day. The authors used a generalized additive Poisson model including Fourier series adjustments for season, linear and quadratic terms for temperature, dew point, and time trend. The relative risk of respiratory disease was found to be about 1.12 (1.01 to 1.24) corresponding to an increase of 100 $\mu g/m^3$ of PM_{10}. Associations with ozone were also found to be significant.

Schwartz (1995a) studied respiratory hospital admissions (ICD9-460-519) for elderly patients in New Haven and Tacoma during 1988 to 1990. For New Haven, daily PM_{10} exposure estimates were averaged from all monitoring stations giving data. The mean PM_{10} was 41, the 10th percentile 19 and the 90th percentile 67 $\mu g/m^3$. The mean O_3 was 29, the 10th percentile, and the 90th percentile 45 ppb. The mean SO_2 was 30 ppb, the 10th percentile 9 and the 90th percentile 61. A Poisson log-linear regression model with a 19 day moving average filter was used to analyze the data. Temperature and dew point were adjusted for in the moving average.

The relative risk for respiratory hospital admissions for a 50 μg/m^3 increase in PM_{10} was 1.06 (1.00, 1.13). Using a two day lag SO_2 term in the model, the RR was 1.07 (1.01, 1.14). The same analysis was run for the Tacoma data. The RR for respiratory hospital admissions for a 50 μg/m^3 increase in PM_{10} was 1.10 (1.03, 1.17). Using a two day lag SO_2 term in the model, the RR was 1.11 (1.02,1.20).

Schwartz and Morris (1995) studied ischemic heart disease hospital admissions (ICD9 410 to 414, 427 and 428) for the elderly in Detroit from 1986 to 1989. There were from 2 to 11 PM_{10} monitoring stations operating during the study period, and data were available for 82% of possible days The mean PM_{10} was 48 μg/m^3, the 10th percentile 22 and the 90th percentile 82. The mean SO_2 was 25 ppb, the 10th percentile 11 and the 90th percentile 44. A Poisson auto-regressive model using GEE was used to analyze the data with dummy variables for temperature, month, and linear and quadratic time trend. The relative risk ratio for hospital admissions for ischemic heart disease for a 32 μg/m^3 increase in PM_{10} was 1.018 (1.005, 1.032). Using O_3, CO and SO_2 in the model resulted in a relative risk of 1.016 (1.002, 1.030).

Cardiac and respiratory hospital admissions in 168 acute care hospitals in Ontario, Canada for 1983 to 1988 calendar years were studied by Burnett et al. (1995). The cardiac admissions were defined as ICD9 codes 410, 413, 427, and 428, and the respiratory admissions as codes 466, 480 to 486, 490 to 494 and 496. No other age restrictions were given. Twenty-two monitoring stations were used to estimate daily O_3 and sulfate fraction data. Meteorological information came from 10 different stations. The daily fluctuations in admissions were related to the pollution and meteorological data after subtracting a 19 term linear trend as discussed by Shumway et al. (1983). The rates were analyzed using a random effects model, where hospitals were assumed to be random. The estimates were obtained using the generalized estimating equations (GEE) of Liang and Zeger (1986). The sulfate fraction, O_3, and temperature were all predictors of hospital admissions, with O_3 more significant than the sulfate fraction. The models tended to predict about a 3 to 4% increase in respiratory admissions and about a 2 to 3% increase in cardiac admissions with about a 13 μg/m^3 increase in the concentration of sulfate fraction.

Hospital Admission Studies Summary

Hospitalization data can provide a measure of the morbidity status of a community during a specified time frame. Hospitalization data specific for respiratory illness diagnoses, or more

specifically for COPD and pneumonia, provide an index of respiratory status. Such studies provide an outcome measure that relates to mortality studies for total and specified respiratory measures as were summarized earlier in Tables 12-8 through 12-11. The separate panels in Figure 12-1 compare the studies by their relative risk (along with 95% confidence intervals). Many of the same factors and concerns related to the mortality studies are at issue for these studies also.

Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The admission studies of respiratory disease show a similar effect. The hospitalization studies in general use similar analysis methodologies, and the majority of the COPD and pneumonia papers are written by a single author. There is a suggestion of a relationship to heart disease, but the results are based on only two studies and the estimated effects are smaller than those for other endpoints. Overall, these studies are indicative of morbidity effects being related to PM. They are also supportive of the mortality findings, especially with the more specific diagnosis relationships.

While a substantive number of hospitalizations for respiratory related illnesses occur in those $\geq$65 years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the hospitalization studies restricted their analysis by age of the individuals. These studies are indicative of health outcomes related to PM for individuals $\geq$65 years of age, but did not examine other age groups that would allow directly comparable estimates as some mortality studies did. The limited analyses examining young age groups, especially children $\leq$14 years of age constrain possible conclusions about this age group.

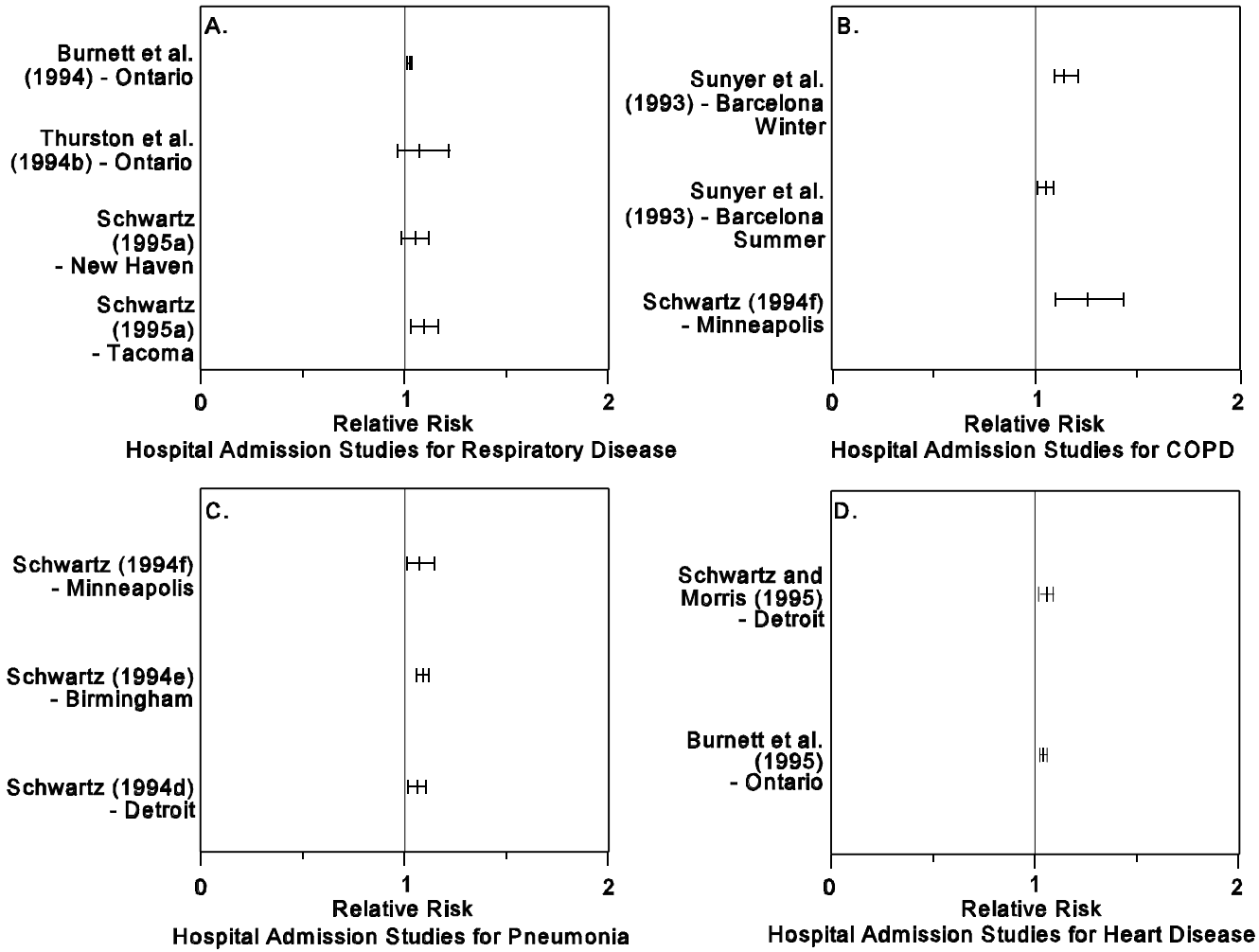

Figure 12-1. Relative risk for hospital admission for respiratory diseases, Chronic Obstructive Pulmonary Disease (COPD), pneumonia, and heart disease for a 50 $\mu g/m^3$ increase in PM_{10} (or equivalent) as shown for several studies.

Schwartz (1995b) reviewed the hospital admission and mortality studies of particulate matter and ozone. The hospitalization results were based on the studies of Thurston et al., (1992), Schwartz (1994e), Burnett et al. (1994), Schwartz (1994f), Sunyer et al. (1993), Schwartz (1994d), and Burnett et al. (1995). Summary tables in Schwartz (1995b) for all respiratory admissions showed relative risks ranging from 1.10 to 1.20 per 100 $\mu g/m^3$ TSP (or equivalently, 1.05 to 1.10 per 50 $\mu g/m^3$ PM_{10}). Summary tables for COPD admissions showed relative risks ranging from 1.15 to 1.57 per 100 $\mu g/m^3$ TSP (or equivalently, 1.07 to 1.25 per 50 $\mu g/m^3$ PM_{10}). Schwartz (1996b) argues that because there is no significant heterogeneity in the relative risks across studies that:

> "This suggests that confounding by other pollutants or weather is not the source of these associations, since the coincident weather patterns and levels of other pollutants varied greatly across the studies. In particular, studies in the western United States (Spokane, Tacoma) had very low levels of sulfur dioxide, and much less humidity than [sic] in the eastern United States locations."

However, tests for homogeneity are known to have very little power against specific alternatives, and so this conclusion may not be appropriate (Hunter and Schmidt, 1989). Even when SO_2 levels are low, anthropogenic PM from combustion or industrial emissions may be accompanied by other criteria pollutants such as CO, O_3, or NO_x.

Air Quality Criteria for Ozone and Other Photochemical Oxidants (U.S. Environmental Protection Agency, 1996) examines several of these same studies for an O_3 effect and concludes that collectively the studies (Thurston et al., 1992, 1994b; Burnett et al., 1994; Delfino et al., 1994a; Schwartz, 1994e,d,f) indicate that ambient O_3 often has a significant effect on hospital admission for respiratory causes with a relative risk ranging from 1.1 to 1.36/100 ppb O_3. Schwartz (1995b) reports a range of 1.04 to 1.54/100 mg/m^3 O_3 and notes that these results are from two pollutant models (PM and O_3) and, while the RR for O_3 are somewhat lower than PM, the same pattern of a larger RR for COPD compared to all respiratory admissions is observed. Also, Schwartz (1995a) in New Haven and Tacoma stated that two pollutant models were examined to determine which pollutant made independent contributions to explaining respiratory hospital admission. The PM_{10} and O_3 associations appeared to be independent of each other, with no reduction in the relative risk for one pollutant after control for the other. Additionally, while there is a suggestion of an effect for PM and heart disease, none was reported for O_3.

The hospitalization studies usually compared daily fluctuations in admissions about a long term (e.g., 19 day) moving average. These fluctuations were regressed on PM estimates for the time period immediately preceding or concurrent with the admissions. Some authors considered lags up to 5 days, but the best predictor usually was the most recent exposure. Some morbidity outcomes associated with hospitalization may be appropriately associated with concurrent admission, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined for hospital admissions related to PM exposures.

12.3.2.2 Respiratory Illness Studies

Respiratory illness and the factors determining its occurrence and severity are important public health concerns. This section discusses epidemiologic findings relating estimates of PM exposure to respiratory illness. This effect is of public health importance because of the widespread potential for exposure to PM and because the occurrence of respiratory illness is common (Samet et al., 1983; Samet and Utell, 1990). Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage (Glezen, 1989; Samet et al., 1983; Gold et al., 1989).

The PM studies generally used several different standard respiratory questionnaires that evaluated respiratory health by asking questions about each child's and adult's respiratory disease and symptom experience daily, weekly or over a longer recall period. The reported symptoms and diseases characterize respiratory morbidity in the cohorts studied. A brief discussion of aspects of epidemiology of respiratory morbidity provides a background for studies examining PM exposure in relation to respiratory health. Respiratory morbidity typically includes specific diseases such as asthma and bronchitis, and broader syndromes such as upper and lower respiratory illnesses.

Asthma is characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to non-specific stimuli (National Institutes of Health, 1991). Asthma patients develop clinical symptoms such as wheezing and dyspnea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms associated with decreased levels of

various measures of forced expiratory volume. Although viral respiratory tract infections are common asthma triggers, especially in young children (National Institutes of Health, 1991), symptoms such as wheezing may occur without an infectious cause.

Overall, an estimated 4.9% of the total U.S. population or over 12 million people, have asthma (National Center for Health Statistics, 1994c). The prevalence of physicians diagnosed asthma among children under age 18 is 6.3/100 (National Center for Health Statistics, 1994c). From 1982 through 1992, asthma mortality among persons aged 5 to 34 years (for whom the diagnosis is likely most accurate) increased 42%, from 3.4 per 1 million population (401 deaths) to 4.9 per 1 million population (569 deaths) (U.S. Centers for Disease Control, 1995).

Chronic bronchitis in adults is defined as a clinical disorder characterized by excessive mucous secretion in the bronchial tubes with an associated chronic productive cough on most days for a minimum of 3 months of the year for not less than 2 successive years (American Thoracic Society, 1962). Chronic mucus hypersecretion can occur with or without obstruction. When the obstruction is fixed, there is often associated emphysema. The diagnosis can only be made after excluding other disorders with similar symptoms. Symptoms and findings observed in children with physician-diagnosed chronic bronchitis commonly include recurrent respiratory infections and wheezing, with chronic phlegm production and chronic cough being less prevalent (Burrows and Lebowitz, 1975). Respiratory syncytial virus (RSV) and parainfluenza virus are isolated in cases of bronchitis (Chanock and Parrott, 1965), but symptoms of bronchitis may occur without an infectious cause.

Viral respiratory illnesses can be subdivided by predominant anatomic site of involvement in the respiratory tract: rhinitis (the common cold), pharyngitis, laryngitis, laryngotracheo bronchitis (croup), tracheobronchitis, bronchiolitis, and pneumonia. In many instances, signs and symptoms referable to more than one site (e.g., pharyngitis, laryngitis, and rhinitis) may occur at the same time in the same patient.

Rhinoviruses lead the list as the most common group of viruses that cause acute upper respiratory illness (URI) in adults and children. Other common viruses include coronaviruses, parainfluenza virus, respiratory syncytial virus, and influenza virus. The number of URI acquired per year decreases with age. Infants and preschool children have the highest incidence (4 to 8 colds per year), and adults generally have two to five colds per year. Typically, symptoms and responses on respiratory questionnaire for upper respiratory illness include throat

irritation, acute cough, cough with phlegm, wheeze, runny nose, breathing difficulty, fever, and earache.

Acute lower respiratory illnesses are generally classified into one of four clinical syndromes: croup (laryngotracheobronchitis), tracheobronchitis, bronchiolitis, and pneumonia (Glezen and Denny, 1973; Wright et al., 1989; McConnochie et al., 1988). In a study in Tucson, the most common diagnosis during the first year of life was bronchiolitis, which accounts for 60% of all lower respiratory illness (Wright et al., 1989). The most common signs and symptoms associated with lower respiratory illnesses were wet cough (85%), wheeze (77%), tachypnea (48%), fever (54%), and croupy cough (38%) as reported by Wright et al. (1989). A few infectious agents are presumed to cause the majority of childhood lower respiratory illness. Bacteria are not thought to be common causes of lower respiratory illness in nonhospitalized infants in the United States (Wright et al., 1989). Seventy-five percent of the isolated microbes were one of four types: RSV, parainfluenza virus types 1 and 3, and *Mycoplasma pneumoniae* (Glezen and Denny, 1973; McConnochie et al., 1988). Respiratory syncytial virus is particularly likely to cause lower respiratory illness during the first two years of life. More than half of all illnesses diagnosed as bronchiolitis, for which an agent was identified, were positive for RSV (Wright et al., 1989). Wright et al. (1989) noted that studies that rely on parental reports of symptoms may underestimate illness. Asking parents about illnesses at the end of the first year of life revealed that one-third of them failed to report illnesses diagnosed by pediatricians.

Various studies of lower respiratory illness have reported rates based on visits to physicians ranging from about 20 to 30 illnesses/100 children in the first year of life (Glezen and Denny, 1973; Wright et al., 1989; Denny and Clyde, 1986; McConnochie et al., 1988). Glezen and Denny (1973) reported that the rate for lower respiratory illnesses ranged from 24/100 person-years in infants under one year of age and decreased steadily each year through the preschool years, tending to level off in school children (age 12 to 14 years) to about 7.5 illnesses/100 person-years. Several factors affect the rate of lower respiratory illness in children, including age, immunologic status, prior viral infections, siblings of early school age, level of health, SES (Chanock et al., 1989), day care attendance, home dampness and humidity, environmental tobacco smoke, NO_2, PM, and other pollutants. Rates also depend on method of illness ascertainment. Studies in the United States (Wright et al., 1989; Denny and Clyde, 1986;

McConnochie et al., 1988) indicated that the overall pattern and incidence of lower respiratory illness is consistent in different geographic regions during the two decades covered by the studies, suggesting that diagnosis and infectious agents have changed little in that time period. Lower respiratory illness remains one of the major causes of childhood morbidity in the United States (McConnochie et al., 1988).

Over the past 4 decades, a large body of epidemiologic evidence has accumulated that indicates that respiratory illness events in childhood (mostly viral) are important determinants (risk factors) for the future risk of chronic respiratory symptoms and disease in adult life (Samet et al., 1983; Denny and Clyde, 1986; Britten et al., 1987; Glezen, 1989; Gold et al., 1989). Based on such data, it seems likely that any factor such as PM that could be responsible for increasing the risk of childhood respiratory illness and symptoms would be of considerable public health importance not only with regard to immediate morbidity, but also in relation to its contribution to chronic respiratory disease morbidity later in life.

Studies of Respiratory Illness in Children

Schwartz et al. (1994) analyzed respiratory symptoms in children from the Harvard Six Cities Studies. The cities included Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; and Topeka, KS. Daily diaries of respiratory symptoms were collected from the parents of 1844 school children for one year starting in September, 1984. A centrally located residential monitor measured SO_2, NO_2, and O_3 on a continuous basis, $PM_{2.5}$ and PM_{10} were collected by a dichotomous sampler ,and aerosol acidity was measured daily. A multiple logistic regression model was used to analyze the data, adjusting for serial correlation by autoregressive terms estimated using the generalized estimating equations of Liang and Zeger (1986). The only weather variable included in the model was temperature, using both linear and quadratic terms.

In order to avoid the seasonal component of respiratory illness, the analysis was restricted to the months of April through August. During this period the $PM_{2.5}$ values had a median value of 18 $\mu g/m^3$ with 10th and 90th percentile values of 7.2 and 37.0 $\mu g/m^3$. The PM_{10} values had a median value of 30 $\mu g/m^3$ with 10th and 90th percentile values of 13 and 53 $\mu g/m^3$. Sulfate fractions were estimated from the $PM_{2.5}$ filters. The strongest relationships for cough were found with PM_{10} and O_3, and these effects appeared to be independent of each other. An

increase of 30 μg/m^3 in PM_{10} was associated with an odds ratio for cough of 1.28 (1.07 to 1.54). Fitting a non-parametric Generalized Additive Model showed that cough incidence increased monotonically with PM_{10} concentration, and there was no evidence of non-linearity. Lower respiratory symptoms (LRS) were also related to all pollutants except acidity. Strongest relationships were found with PM_{10} and sulfate fraction, and these effects appeared to be independent of each other. An increase of 30 μg/m^3 in PM_{10} was associated with an odds ratio for lower respiratory symptoms of 1.53 (1.20 to 1.95). There was no evidence of non-linearity, as shown in Figure 12-2. Comparable analyses for SO_2 and H^+ are shown in Figures 12-3 and 12-4. Note that these curves show an inconsistent relationship at lower exposure estimates. Although these non-parametric models do not provide confidence intervals, it is clear that the relationship between cough and PM_{10} is stronger than for either SO_2 or H^+.

Pope et al. (1991) studied respiratory symptoms in asthmatic school children in the Utah Valley. Participants were selected from samples of 4th and 5th grade elementary students in 3 schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon, Utah and were restricted to those who responded positively to one of: (a) ever wheezed without a cold; (b) wheezed for 3 days out of a week for a month or longer; (c) had a doctor say the "child has asthma". This resulted in 34 subjects who were included in the final analyses. PM_{10} monitors operated by the Utah State Department of Health collected 24 h PM_{10} samples from midnight to midnight (range 11 to 195 μg/m^3) with an average of approximately 46 μg/m^3. There was limited monitoring of SO_2, NO_2, and O_3. Lower respiratory disease was defined as the presence of at least one of: trouble breathing, dry cough, or wheezing. A fixed effects logistic regression analysis was calculated using each person as his own control and low temperature as a covariate. Estimated odds ratios for upper respiratory disease per PM_{10} increase of 50 μg/m^3 was 1.20 (1.03, 1.39); for lower respiratory illness, it was 1.28 (1.06, 1.56).

Pope et al. (1991) also studied asthmatics aged 8 to 72 in the Utah Valley, selected from those referred by local physicians. This resulted in 21 subjects who were included in the final analysis. The same air quality data were used. Lower respiratory disease was

Figure 12-2. Relative odds of incidence of lower respiratory symptoms (LRS) smoothed against 24-h mean PM_{10} ($\mu g/m^3$) on the previous day, controlling for temperature, day of the week, and city.

Source: Schwartz et al. (1994)

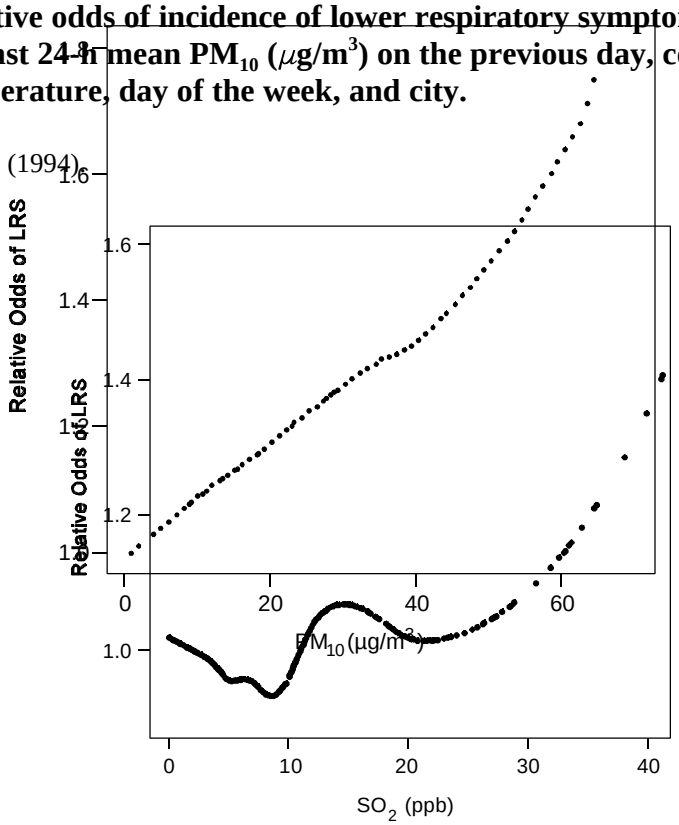

Figure 12-3. Relative odds of incidence of lower respiratory symptom (LRS) smoothed against 24-h mean sulfur dioxide (SO_2) concentration on the previous day, controlling for temperature, city, and day of the week.

Source: Schwartz et al. (1994)

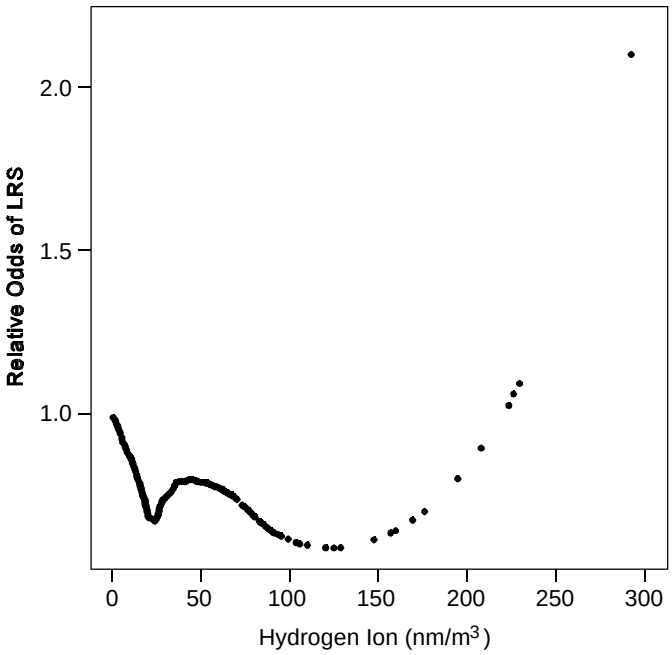

Figure 12-4. Relative odds of incidence of lower respiratory symptom smoothed against 24-h mean hydrogen ion concentration on the previous day, controlling for temperature, city, and day of the week.

Source: Schwartz et al. (1994)

defined the same for this group of subjects. A fixed effects logistic regression analysis was calculated using each person as his own control and low temperature as a covariate. The estimated odds ratio for upper respiratory disease per PM_{10} increase of 50 μg/m^3 in PM_{10} was 0.99 (0.81, 1.22). For lower respiratory illness, it was 1.01 (0.81, 1.27).

In a follow up study, Pope and Dockery (1992) enrolled non-asthmatic symptomatic and asymptomatic children in the Utah Valley, selected from samples of 4th and 5th grade elementary students in three schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon Utah. A questionnaire identified 129 children who were mildly symptomatic and 60 were selected. An additional 60 with no symptoms were recruited. PM_{10} monitors operated by the Utah State Department of Health collected 24 h samples from midnight to midnight; PM_{10} values averaged 76 μg/m^3 during the study period and ranged from 7 to 251 μg/m^3. No SO_2 and limited NO_2 and O_3 monitoring were conducted. Low temperature was used to adjust for weather, but no adjustment was made for humidity. Upper respiratory symptoms had a logistic

regression coefficient of .00519 (.00203) and lower respiratory symptoms had a coefficient of .00658 (.00205) in the symptomatic sample using a 5-day moving average of PM_{10}. These correspond to odds ratios of 1.30 and 1.39 respectively for an increase of 50 $\mu g/m^3$ in PM_{10}. No consistent effects were seen in the asymptomatic sample, although all effects tended to increase with PM. Only minimum temperature was used to adjust for weather.

Ostro et al. (1995) studied a panel of 83 African-American asthmatic children aged 7 to 12 recruited from four allergy and pediatric clinics in central Los Angeles and two asthma camps in the summer of 1992. The analysis focused on the daily reporting of respiratory symptoms including shortness of breath, cough, and wheeze. Daily air monitoring at three fixed sites included O_3, PM_{10}, NO_2, and SO_2. PM_{10} levels ranged from 20 to 101 $\mu g/m^3$ and O_3 from 10 to 160 ppb. Daily temperature, humidity, rainfall, pollens and molds were also used as covariates. A logistic regression allowing for repeated measures with variances estimated by generalized estimating equations was used to estimate effects of the pollutants and covariates. Both PM_{10} and O_3 were associated with increased shortness of breath, and the authors could not separate the effect of the two pollutants. The odds ratio for an increase of 56 $\mu g/m^3$ PM_{10} was 1.58 (1.05, 2.38). No effects were seen with cough or wheeze.

Schwartz et al. (1991a) analyzed acute respiratory illness in children in five German communities. Children's hospitals, pediatric departments and pediatricians were asked to fill out a short questionnaire for each visit for croup or obstructive bronchitis over a 2-year period. A diagnosis of croup was defined as acute stenotic subglottic laryngotracheitis. Not all doctors reported for the full 2 years—a loss of about 50%. Thus, participation was about 50%. Areas chosen to represent a wide range of air pollution exposure included: Duisburg and Köln in the highly industrialized areas of Northrhine-Westfalia and Stuttgart, and Tubingen/Reutlingen and Freudenstadt in South Germany. One to four TSP monitors were located in each study areas and 24 h measurements were taken of TSP, SO_2, and NO_2. TSP was measured by low volume sampler, NO_2 by chemiluminescence, and SO_2 by the conductometric method, and were expressed in $\mu g/m^3$. Poisson regression analysis as described by McCullagh and Nelder (1983) was used to estimate the effect of pollution on croup and obstructive bronchitis, with adjustments for serial correlation using the method of Zeger and Liang (1986). The model included terms for season (annual and biannual sine and cosine terms), weather (temperature and relative humidity), and drop-outs. Logistic regression coefficients estimated from the Poisson

regressions gave values of 0.1244 admissions/log(TSP) (.0309), 0.4161 (.156) for NO_2, and 0.0831 (.0352) for SO_2. The log TSP coefficient was not significant when either NO_2 or SO_2 were included in the model.

Hoek and Brunekreef (1993) and Hoek (1992) studied a general population sample of 112 children aged 7 to 12 who lived in the nonindustrial town, Wageningen, NL. Acute respiratory symptoms of the children were recorded in a diary by their parents, including throat irritation, cough, cough with phlegm, wheeze, runny nose, and a variety of other symptoms. PM_{10} was measured daily (3PM to 3PM) with an inlet design similar to the Sierra Anderson 241 dichotomous sampler. SO_2 was measured using fluorescence, and NO_2 was measured using chemiluminescence. Logistic regression analyses including first order autoregressive terms were used to analyze the data and included ambient temperature and day of study as covariates. The PM_{10} coefficient for any upper respiratory illness was 0.0026 (0.0013). This corresponds to an odds ratio of 1.14 (95% confidence interval of (1.00 to 1.30) for an increase of 50 $\mu g/m^3$ PM_{10}. Most other coefficients were not significant.

Braun-Fahrländer et al. (1992) studied daily respiratory disease symptoms in preschool children in 4 areas of Switzerland. A sample of 840 children was chosen from Basel and Zurich. One-twelfth of the sample was recruited each month from November 1985 to November 1986. A physician conducted a standardized questionnaire with the parents. Parents recorded daily symptoms including cough without runny nose, breathing difficulty, and fever with earache and sore throat. TSP was measured daily (method not given) and NO_2 by Palmes tubes both outside the apartment and inside the room where the child stayed most frequently. Children lived within 6 km of an outdoor monitor which measured TSP, NO_2, SO_2, and O_3. Multiple logistic regression analysis was used to explain differences in upper respiratory symptom incidence. Analysis terms included temperature, season, city, and a risk strata based on a cross-sectional analysis. Variances were adjusted using the method of Liang and Zeger (1986). The TSP coefficient for upper respiratory symptoms was 0.00454 (0.00174), corresponding to an odds ratio of 1.57 per TSP increase of 100 $\mu g/m^3$. Neither NO_2, SO_2, or O_3 were significant.

Hoek and Brunekreef (1994) studied pulmonary function and respiratory symptoms in more than 1000 children in 4 towns in the Netherlands. Children aged 7 to 11 in Deurne, Enkhuizen, Venlo, and Nijmegen were studied during one of three winters (1987/88, 1988/89, 1989/90). During the study, respiratory symptoms data were collected daily by diary. PM_{10} was

measured daily (3PM to 3PM) with an instrument inlet design similar to the Sierra Anderson 241 dichotomous sampler, SO_2 by fluorescence, and NO_2 by chemiluminescence. Separate logistic regressions were performed for 9 locations (six groups of subjects of Deurne and one in each other town) using a first order autoregressive model. The coefficients were combined using the inverse variance weighting method. The odds ratio for the incidence of cough associated with 100 $\mu g/m^3$ PM_{10} increase was 1.10 (0.67,1.79). PM_{10} odds ratios for upper and lower respiratory illness were also not statistically significant. Nor was the incidence of acute respiratory symptoms significantly related to PM_{10}, SO_2, NO_2, or sulfate.

In a winter study by Roemer et al. (1993) of children with chronic respiratory symptoms, parents of children in grades 3 to 8 in two small nonindustrial towns in the Netherlands were given questionnaires about respiratory symptoms. Seventy-four of the 131 children with positive responses (cough or shortness of breath) were included in the study. PM_{10} was measured daily using an instrument inlet design similar to the Sierra Anderson 241 dichotomous sampler. SO_2, NO_2, and black smoke were also measured. Several symptoms including asthma attack, wheeze, and cough were marginally associated with PM_{10}. The logistic regression coefficient for wheeze was .00224 (.00115) per unit increase in the same day's PM_{10} level. The coefficient for broncho-dilator use was .00210 (.00085). SO_2 and black smoke were also marginally related to several of the symptoms.

Hoek and Brunekreef (1995) studied respiratory symptoms in 300 children aged 7 to 11 years in Duerne and Enkhuizen, The Netherlands. The study was designed as an ozone study, but SO_2, NO_2, and PM_{10} were also measured (PM_{10} ranged 13 to 124 $\mu g/m^3$; O_3 ranged 22 to 107 ppb). A symptom diary similar to that used in the Harvard Six Cities Study was used to obtain daily information on cough, phlegm, wheeze, runny nose, and other respiratory symptoms. A multiple logistic model with first order autoregressive residuals was used. Additional analyses using ARIMA models to allow for autocorrelation confirmed results of the logistic analyses. Nearly all logistic regression coefficients were non-significant and negative. The analyses of cough in Deurne gave an estimated odds ratio of 0.93 for a 50 $\mu g/m^3$ increase in PM_{10} on the same day. Analyses of other endpoints, lag times, and pollutants gave similar results.

Relationships between air pollution indices for 84 standard metropolitan statistical areas (SMSA`s) mostly of 100,000 to 600,000 people in size and indices of acute morbidity effects were studied by Ostro (1983), Hausman et al. (1984), and Ostro (1987), using data derived from

the National Center for Health Statistics (NCHS) Health Interview Survey (HIS) of 50,000 households comprising about 120,000 people. Ostro (1983) used HIS data to assess the prevalence of illness and illness-related restrictions in activity in the United States. Data on either restricted activity days (RADs) or work loss days (WLDs) were aggregated over a year, and correlated with annual TSP levels, controlling for temperature, wind, precipitation, population density, and smoking. Using the 1976 survey, a significant relationship between TSP and both outcomes was found, with RAD's being more significant. Sulfate fractions were not significantly related to either outcome. Ozone was not measured. The explained variation was much higher for RADs than for WLDs. The average of air pollution monitors for each city was used, rather than aerometric data aggregated for smaller geographic units in relationship to individuals residing nearby for whom HIS data were included in the analysis. Hausman et al. (1984) analyzed the same data, but used Poisson regression analysis using a fixed effects model that compared deviations from the city mean levels of illness and short-term pollution as the exposure variable. Significant associations between 2-week average TSP levels and RADs or WLDs were found. The magnitude of the within city effects was similar to the magnitude of the between city effects seen earlier. Demographic factors were controlled for on an individual basis, along with climatic conditions.

Ostro (1987) applied the Hausman et al. (1984) techniques to analyze HIS results from 1976 to 1981 in relation to estimates of fine particle (FP) mass. That is, for adults aged 18 to 65, days of work loss (WLDs), restricted activity days (RADs) and respiratory-related restricted activity days (RRADs) measured for a 2-week period before the day of the survey were used as measures of morbidity and analyzed in relation to estimated concurrent 2-week averages of FP or lagged in relation to estimated 2-week FP averages from two to four weeks earlier. The FP estimates were produced from the empirically derived regression equations of Trijonis. These equations incorporated screened airport data and 2-week average TSP readings at population-oriented monitors, using data taken from the metropolitan area of residence. Various potentially confounding factors (such as age, race, education, income, existence of a chronic health condition, and average 2-week minimum temperature) were controlled for in the analyses. The morbidity measures (WLDs, RADs, RRADs), for workers only or for all adults in general, were consistently found to be significantly ($p < 0.01$ or < 0.05) related to lagged FP estimates (for air quality 2 to 4 weeks prior to the health interview data period), when analyzed for each of the

individual years from 1976 to 1981. However, less consistent associations were found between the health endpoints and more concurrent FP estimates.

Ostro and Rothschild (1989) studied acute respiratory morbidity based on an analysis of 1976 to 1981 HIS data. Ozone measurements were taken from EPA's SAROAD monitoring network, and FP measurements were estimated from airport visibility data. The endpoints of the analysis included minor restrictions in activity and work loss. Using a multiple regression analysis, both endpoints showed a relationship to FP.

School Absences Studies

Most school absences are due to acute conditions (Klerman, 1988). Respiratory conditions are the most frequent cause, particularly influenza and the common childhood infectious diseases. School absences are also caused by injuries, digestive system conditions and ear infections. Kornguth (1990) notes the following characteristic of school absent children: (1) as mothers level of education or family income increased the likelihood of their children being absent decreased; and (2) days absent due to illness are related to source of medical care and to type of health insurance coverage. Children with a wide range of chronic illnesses miss more school than their healthy peers. There is only tentative evidence that school absent rates of individual children vary directly with the severity of their health problem (Weitzman, 1986). Parcel et al. (1979) found that children with asthma have a significantly higher absentee rate than do nonasthmatic children. Children who smoke and whose parents smoke are more likely to be absent from school for minor ailments (Charlton and Blair, 1989). Whether this increased likelihood of absence is due to genuine health problems, or to a generally negative attitude to school in children who take up smoking to boost their self-esteem, is unclear.

Most excessive school absence is probably the result of factors outside the health care sphere (Klerman, 1988). Chaotic family environments, lack of achievement motivation, understaffed and uninviting schools, and other societal problems, are undoubtedly the major reason for absenteeism. Excessive school absence is a profound educational and social problem in the United States (Weitzman et al., 1986). Despite the fact that the majority of school absences are reported as being health related, data suggest that demographic and educational characteristics of students have a much greater influence on absence behavior than do health-related factors. Since school absence rates reflect both health and non-health related factors, it is

important that investigators recognize the nonspecific nature of the measure and account for non-health related influences appropriately (Weitzman, 1986). Such non-health related potential problems with the data include the following: data are difficult to collect, individual data as compared to aggregate data; different coding in schools for tardy or leaves school early for sickness; and, records may not be computerized at school, making retrospective studies more difficult (Weitzman, 1986).

Ransom and Pope (1992) studied elementary school absences in connection with the steel strike in the Utah Valley. Data for school absences from 1985 to 1991 were obtained from two sources: (1) district-wide attendance averages by grade level from the Provo School District, and (2) daily absenteeism records from the Northridge Elementary School in Orem. The Northridge School was much closer to the steel mill than were the schools in the Provo School District. Daily PM_{10} measurements were made at three sites (Linden, Provo, and Orem), but only the Linden site collected daily measurements for the entire time period of the study. Some SO_2 and O_3 measurements were available, but these values tended to be well below the National Ambient Air Quality standards. Meteorological information was available from the Brigham Young University weather station. Regression analyses were conducted, taking into account several covariates including month of study, snowfall, Christmas and Thanksgiving holidays, and low temperature. The best PM_{10} predictor was a 4-week moving average. A highly significant increase of about 2% in the absence rates (absolute increase) for an increase of 100 $\mu g/m^3$ increase in the 4-week average PM_{10} was found for both sets of data, and the coefficient was similar even when a dummy variable was added for the strike. No adjustments were made for periods of increased influenza cases.

Studies of Respiratory Illness in Adults

Lawther et al. (1970) reported on studies carried out from 1954 to 1968 mainly in London, using a diary technique for self-assessment of day-to-day changes in symptoms among bronchitic patients. A daily illness score was calculated from the diary data and related to BS and SO_2 levels and weather variables. Pollution data for most of the London studies were mean values from the group of sites used in the mortality/morbidity studies of Martin (1964). In early years of the studies, when pollution levels were generally high, well defined peaks in illness score were seen when concentrations of either BS or SO_2 exceeded 1,000 $\mu g/m^3$. With later

reductions in pollution, the changes in condition became less frequent and of smaller size. From the series of studies as a whole, up to 1968, it was concluded that the minimum pollution levels associated with significant changes in the condition of patients was a 24-h mean BS level of ~250 $\mu g/m^3$ together with a 24-h mean SO_2 concentration of ~500 $\mu g/m^3$ (0.18 ppm). A later study reported by Waller (1971) showed that, with much reduced average levels of pollution, there was an almost complete disappearance of days with smoke levels exceeding 250 $\mu g/m^3$ and SO_2 levels over 500 $\mu g/m^3$ (0.18 ppm). As earlier, some correlation remained between changes in the conditions of the patients and daily concentrations of smoke and SO_2, but the changes were small at these levels and it was difficult to discriminate between pollution effects and those of adverse weather. The analysis of the Lawther et al. (1970) study was made prior to the availability of current statistical methods such as poisson regression using generalized estimating equations. The large differences seen by Lawther et al. (1970) at high levels would undoubtedly remain significant regardless of the analysis technique.

Dusseldorp et al. (1994) studied respiratory symptoms in 32 adults living near a large steel plant in Wijk aan Zee, The Netherlands. During the study period PM_{10} levels ranged from 36 to 137 $\mu g/m^3$. Diary information on acute respiratory symptoms, medication use, and presence of fever was collected. Peak flow measurements were also taken. The study was conducted from 11 October 1993 to 22 December 1993, and the average number of days per subject was 66. A logistic regression model was used and to control autocorrelation, a linear time series model was also fitted. Both models gave similar results and so the logistic regression coefficients converted to odds ratios for 100 $\mu g/m^3$ were reported. These were converted to odds ratios for 50 $\mu g/m^3$. The odds ratio for cough on PM_{10} (lag zero) was 1.31 (0.9, 1.76). The other endpoints of phlegm, shortness of breath and wheeze showed lesser effects. Using PM_{10} lagged one, two, and three days showed little effect.

Lebowitz et al. (1982) studied 117 families in Tucson, AZ selected from a stratified sample of families in geographical clusters from a representative community population included in an ongoing epidemiologic study. Both asthmatic and non-asthmatic families were evaluated over a 2-year period using daily diaries. The health data obtained were related to various indices of environmental factors derived from simultaneous micro-indoor and outdoor monitoring in a representative sample of houses for air pollutants, pollen, fungi, algae and climate. Monitoring of air pollutants and pollen was carried out simultaneously. Two-month averages of indoor TSP

ranged from 2.1 to 169.6 $\mu g/m^3$. Cyclone measurements of respirable particulate (RSP) ranged from below minimum detectable limits up to 28.8 $\mu g/m^3$; CO and NO_2 measurements were also taken, but no $S0_2$ monitoring was reported. This appears to be one of the few studies monitoring indoor air. TSP and pollen were reported to be related to symptoms in both asthmatics and non-asthmatics, but the authors reported that the statistical analyses used were all qualitative (because of low sample size) and statistical significance was not computed.

Whittemore and Korn (1980) studied asthmatics in seven communities in the Los Angeles area. Panelists were located by consulting local physicians and were followed for 34 weeks from May 7 to December 30 in the years 1972 to 1974 from the communities of Santa Monica, Anaheim, Glendora, Thousand Oaks, Garden Grove, and Covina. Dairies were filled out weekly by the participants who gave daily information on symptoms. Monitoring stations were placed in each community near an elementary school. TSP, RSP, suspended sulfates, suspended nitrates, SO_2, and photochemical oxidants were measured. NO_2 was also measured but the data were determined to be unreliable. Because of the colinearities and measurement errors, only TSP and photochemical oxidants were actually included in the analyses. A logistic model was used for each individual that included the presence of an attack on the previous day, meteorology, day of study, day of week, and pollutants. Regression coefficients were combined using both a fixed and random effects model. Both photochemical oxidants and TSP were found to be significantly related to symptoms, even when the other pollutant was included in the model. The coefficient for TSP for both models was .00079 (standard error not given). This corresponds to an odds ratio of 1.08 for a 100 $\mu g/m^3$ increase in TSP.

Ostro et al. (1991) studied adult asthmatics recruited from clinic patients in Denver. Diagnosis of asthma was based on physical exam confirmed by lung function tests. The panel of 207 recorded daily symptoms and medication use from November 1987 to February 1988. Ambient air pollutants measured were sulfates, nitrates, $PM_{2.5}$, nitric acid, H^+, and SO_2 at a downtown Denver monitor two miles from the clinic. Logistic regression analysis was used with adjustment for autocorrelation by creating an instrumental variable; the final regression used Proc Autoreg in SAS. The coefficient for log($PM_{2.5}$) was .0006 (.0053) for asthma and .0012 (.0043) for cough. H^+ was the only pollutant near statistical significance, having an estimate coefficient of .0031 (.0042) for asthma and .0076 (.0038) for cough. The coefficients

cannot be compared directly with other studies because of the log transformation, and attempts to convert them based on mean values give unreasonable answers.

Ostro et al. (1993) studied respiratory symptoms in non-smoking adults aged 18 or more in Southern California from September 1978 to March 1979. The analysis was restricted to those 321 subjects who completed diaries for the entire 181-day period. The health endpoints included upper respiratory illness, lower respiratory illness, and eye irritation. Air pollution data for the Glendora, Covina, and Azusa areas were obtained from the Los Angeles County Air Pollution Control District Station in Azusa and included O_3, NO_2, SO_2, and sulfate fraction of PM. Temperature, rain, and humidity were used as meteorological covariates. A multiple logistic regression analysis was run using the three health endpoints. Ozone, sulfate fraction, and gas stove use were associated with significant odds ratios for lower respiratory tract illness. The odds ratio for gas stove use, 1.23, was well within the range reported in a meta-analysis of studies of nitrogen oxides by Hasselblad et al. (1992), but COH was not significantly related to lower respiratory illness. Only ozone was related to upper respiratory illness or eye irritation. The author did not report that adjustments were made for serial correlation of the health outcomes.

Acute Respiratory Illness Studies Summary

This category includes several different endpoints, but most investigators reported results for at least two of: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough (See Table 12-12 and Figure 12-5). The following relative risks are all estimated for an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The studies of upper respiratory illness do not show a consistent relationship with PM. Two of the studies showed no effect, three studies estimated an odds ratio near 1.2, and the study of Braun-Fahrländer et al. (1992) estimated the odds ratio of 1.55. Some of inconsistency could be explained by the fact that the studies included very different populations.

The studies of lower respiratory disease gave odds ratios which ranged from 1.10 to 1.28 except for the Schwartz et al. (1994) Six-Cities study, which gave a value over 2.0. Although the lower respiratory disease studies also include a variety of populations, it is difficult to explain the large range of estimates.

The studies of cough were more consistent, having odds ratios ranging from 0.98 to 1.51. Again, the Schwartz et al. (1994) study produced the largest value. The second highest value was that of 1.29 from Pope and Dockery (1992).

All three endpoints had the same general pattern of results. Nearly all odds ratios were positive, and about half were statistically larger than 1. Each endpoint had one study with a very high odds ratio. This can be compared with the hospital admission studies which all resulted in very similar estimates. There are several factors which could account for this. The respiratory disease studies used a wide variety of designs. As a result, the models for analysis were also varied. Finally, the populations included several different subgroups whereas the hospitalization studies tended to include similar populations.

There were fewer studies of respiratory symptoms in adults as compared with those in children. Whittemore and Korn (1980) found a relationship between TSP and asthma attacks in a panel of asthmatics. The estimated effect corresponded to an odds ratio of 1.08 for a 100 $\mu g/m^3$ increase in TSP. However, Ostro et al. (1991) found no relation between asthma or cough with $PM_{2.5}$ in asthmatics in Denver. No other studies estimated quantitative relationships.

12.3.2.3 Pulmonary Function Studies

Pulmonary function studies are part of any comprehensive investigation of possible effects of an air pollutant. Measurements can be made in the field, they are noninvasive, and the reproducability of some lung function measures has been well documented. Also,

TABLE 12-12. ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[2] (Confidence Interval)
Schwartz et al. (1994), study of respiratory symptoms in 6 U.S. cities, 1984-1988	Daily data for PM_{10}, $PM_{2.5}$ at each city	median PM_{10} 30 µg/m^3; 10% tile 13, 90% tile 53. median $PM_{2.5}$ 18 µg/m^3; 10% tile 7, 90% tile 37.	(not given)	Autoregressive logistic regression using GEE	SO_2, median 4 ppb; 10% tile 1 ppb, 90% tile, 18 ppb. NO_2, median 13 ppb; 10% tile 5 ppb; 90% tile 24 ppb O_3.	Temp., day of week, city or residence	All two pollutant models fitted with minimal effect on PM	Cough (PM_{10} lag 1): 1.51 (1.12, 2.05) Upper resp. (PM_{10} lag 2): 1.39 (0.97, 2.01) Lower resp. (PM_{10} lag 1): 2.03 (1.36, 3.04)
Pope et al. (1991), study of students in Utah Valley, winter 1989-1990	PM_{10} data for stations at 3 sites	mean 46 µg/m^3; range 11 to 195 μg/m^3	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, and O_3. Values well below NAAQS.	Variables for temp. and time trend	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.28 (1.06, 1.56)
Pope et al. (1991), study of asthmatic children in Utah Valley, winter 1989-1990	PM_{10} data for stations at 3 sites	mean 46 µg/m^3; range 11 to 195 μg/m^3	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, O_3. Values well below NAAQS.	Variables for low temp. and time trend	none	Upper resp. 0.99 (0.81, 1.22) Lower resp. 1.01 (0.81, 1.27)
Pope and Dockery (1992), symptomatic children in the Utah Valley, winter 1990-1991	PM_{10} data for stations at 2 sites	mean 76 µg/m^3; range 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temp.	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.27 (1.08, 1.49) Cough 1.29 (1.12, 1.48)

TABLE 12-12 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[1] (Confidence Interval)
Pope and Dockery (1992), asymptomatic children in the Utah Valley, winter 1990-1991	PM_{10} data for stations at 2 sites	mean 76 µg/m^3; range 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temp.	none	Upper resp. 0.99 (0.78, 1.26) Lower resp. 1.13 (0.91, 1.39) Cough 1.18 (1.00, 1.40)
Hoek and Brunekreef (1993), respiratory disease in school children aged 7 to 12 in Wageningen, NL, winter 1990-1991	PM_{10} data for 2 to 4 stations	max 110 µg/m^3	(not given)	Autoregressive logistic regression using GEE	Max SO_2 105 µg/m^3; max NO_2 127 µg/m^3	Variable for ambient temp. and day of study	none	Upper resp. 1.14 (1.00, 1.29) Lower resp. 1.06 (0.86, 1.32) Cough 0.98 (0.86, 1.11)
Schwartz et al. (1991a), study of acute respiratory illness in children in five German communities, 1983-1985	Two to 4 monitoring stations in each area measured TSP	medians 17 to 56 µg/m^3; 10% tiles 5 to 34; 90% tiles 41 to 118	0.5 to 2.9	Autoregressive Poisson regression using GEE	median SO_2 levels ranged 9 to 48 µg/m^3, median NO_2 levels ranged 14 to 5 µg/m^3	Most stat. significant terms of day of week, time trend, and weather	none (TSP not stat. significant when NO_2 added to model)	1.26 (1.12, 1.42)
Braun-Fahrländer et al. (1992), study of preschool children in four areas of Switzerland	Daily data for TSP	(not given)	4.4	Logistic regression	SO_2, NO_2, and O_3 levels not given	City, risk strata, season, temperature	none	Upper resp. 1.55 (1.10, 2.24)
Roemer et al. (1993), study of children with chronic resp. symptoms in Wageningen, NL.	Daily data PM_{10}	6 days above 110 µg/m^3	.094 incidence rate	Autoregressive logistic regression	SO_2 and NO_2 means not given	(not given)	none	Cough (not given, probably less than one)

TABLE 12-12 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[2] (Confidence Interval)
Dusseldorp et al. (1994) Study of adults near a Netherlands steel mill	Daily data for PM_{10}, iron, sodium, silicon, and manganese	mean PM_{10} 54 µg/m^3; range 4 to 137	(not given)	Logistic regression	Geometric mean iron 501 ng/m^3; manganese 17 ng/m^3; silicon 208 ng/m^3	(not given)	none	Cough 1.14 (0.98, 1.33)
Ostro et al. (1991), study of adult asthmatics in Denver, Colorado November 1987 to February 1988	Two monitors provided daily measurements of $PM_{2.5}$	22 µg/m^3; range 0.5 to 73 μg/m^3	15 (out of 108)	Autoregressive logistic regression	nitric acid, sulfates, nitrates, SO_2, and hydrogen ion	Day of week, gas stove, min. temp.	none	Cough 1.09 (0.57, 2.10)
Ostro et al. (1993), study of non-smoking adults in Southern California	Apparently one site (Azusa). PM measurements included sulfate and COHS	mean sulfate 8 µg/m^3; range 2 to 37 μg/m^3 mean COHS 12 per 100 ft; range 4 to 26	4.2/person for lower resp., 10.2/person, upper resp.	Logistic regression	ozone, mean = 7 pphm, range = 1 to 28	Temp., none rain humidity	none	Sulfates: Upper resp. 0.91 (0.73, 1.15) Lower resp. 1.48 (1.14, 1.91)
Ostro et al. (1995), study of 83 African-American asthmatic children in Los Angeles	3 sites measured PM_{10}, O_3, NO_2, SO_2	PM_{10} ranged 20 to 101 μg/m^3 mean 56 μg/m^3	Not given	Logistic regression using GEE method	O_3, NO_2, SO_2	Humidity, temp., pollens, molds	O_3	Shortness of breath increase per a 56 μg/m^3 PM_{10} increase was 1.58 (1.05, 2.3). No effect on cough or wheeze.

TABLE 12-12 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[2] (Confidence Interval)
Hoek and Brunekreef (1995), study of respiratory symptoms in 300 children in 2 Netherlands communities	2 sites measured PM_{10}, O_3, sulfate, nitrate	Deane PM_{10} mean 48 $\mu g/m^3$ (range 13-124); Enkhulzen PM_{10} a mean 36 $\mu g/m^3$ (range 11-136)	Cough 5.5, LRS 1.5	Time series analyses (Box-Jenkins approach logistic regression model)	O_3, sulfate, nitrate	Trend, day of week, humidity		Logistic regression coefficient was -.0014 (-.0032, .0004) for PM_{10}. Similar coefficients for LRS, and any respiratory symp.

[1]Both mean and/or range provided as reported in cited paper.
[2]Odds ratio calculated from parameters given in published paper, assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

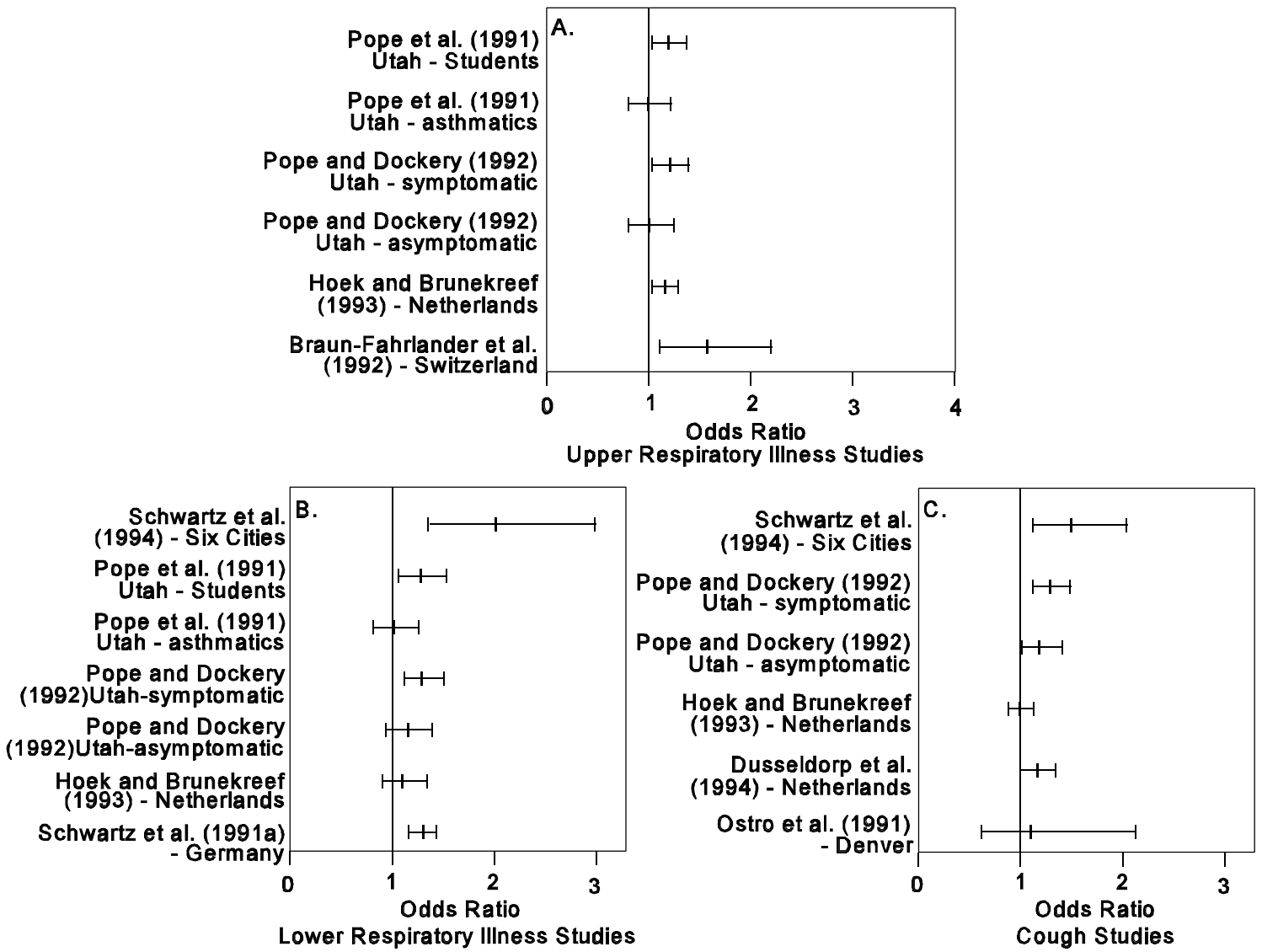

Figure 12-5. Odds ratios for acute respiratory disease (upper respiratory illness, lower respiratory illness, and cough) for a 50 $\mu g/m^3$ increase in PM_{10} (or equivalent) for selected studies.

guidelines for standardized testing procedures reference values, and interpretative strategies exist for lung function tests (American Thoracic Society, 1987, 1991).

Various factors are important determinants of lung function measures. For example, lung function in childhood is primarily related to general stature (as measured by height and, for children, by age). The growth patterns differ between males and females. Compared to girls, boys show larger size-adjusted (usually height or height^2) average values for various measures of lung function (Wang et al., 1993a,b). Moreover, growth of measures derived from forced expiratory maneuvers (e.g., forced vital capacity-FVC and forced expiratory volume one-second-FEV_1) continues for a longer period of time in males, beyond the time when height growth is complete (Wang et al., 1993a,b). Lung function begins to decline with age in the 3rd to 4th decades (Tager et al., 1988) and continues to do so monotonically as people age. Cigarette smoking, the presence of chronic obstructive lung disease, and/or asthma are some factors related to more rapid declines in lung function in adults (Tager et al., 1988; Vedal et al., 1984).

Factors in the environment undoubtedly influence the natural history of the growth and decline of lung function. Several such factors (viral respiratory illness, active smoking and passive exposure to tobacco smoke products) are briefly discussed here.

As in older children and adults, clinically inapparent alterations in lower airway function can occur during upper respiratory infections (URI) in infants (Martinez et al., 1990). Both differences in the caliber or length of the airway and differences in the elasticity of the lungs and chest wall may exist between infants who subsequently have wheezing with a viral lower respiratory tract illness and those who do not have wheezing with a similar illness. Thus the initial airway caliber, length, or both (and perhaps the structure of the lung parenchyma) may predispose infants to wheezing in association with common viral respiratory infection (Martinez et al., 1988; Tager et al., 1993; Martinez et al., 1991; Martinez et al., 1995).

Active smoking is the major risk factor for chronic airflow limitation. As a group, cigarette smokers have more rapid reductions in lung function with age relative to non-smokers. In approximately 15 to 20% of long-term regular smokers, this increased loss of lung function leads to the development of symptomatic chronic obstructive lung disease. Smoking cessation can be associated with recovery of a very small amount of function and a lessening of the rate of

decline of function (Dockery et al., 1983). However, such cessation amongst persons with far advanced chronic obstructive lung disease has little effect on the overall course of the disease.

Passive exposure to products of tobacco smoke generated by parental smoking has consistently been associated with alterations in lung function in infants and children. Maternal smoking, in particular, has demonstrated an exposure-response association with reduced lung function. The extensive body of evidence demonstrating this association has been reviewed by the U.S. Environmental Protection Agency (1992). The issue of passive exposure to tobacco smoke has particular conceptual relevance to the issue of the health effect of ambient PM, since tobacco smoke is a major PM source in indoor environments.

Studies of Pulmonary Function in Children

Dockery et al. (1982) studied changes in lung function in school age children as the result of air pollution episodes in Steubenville, OH — one of the cities in Harvard Six-City Study. Steubenville was known to have large changes in SO_2 and TSP exposures, such occurred in fall, 1978; fall, 1979; spring, 1980; and fall, 1980. During each period, lung function measurements ($FEV_{0.75}$ and FVC) were taken prior to the episode and within a week after the episode. Linear regression was used to estimate the effect of pollution on each child separately. The slopes were summarized by time period and combined into a total summary. The pooled slopes were significantly different from zero for for both $FEV_{0.75}$ and FVC in relation to both TSP and SO_2. The median slope for $FEV_{0.75}$ with TSP was −0.018 ml per $\mu g/m^3$ and for FVC it was −0.081 ml per $\mu g/m^3$.

Brunekreef et al. (1991) further analyzed data from Dockery et al. (1982) on pulmonary function in children in Steubenville, OH as part of the Harvard Six-Cities Study. Linear decreases in forced vital capacity (FVC) with increasing TSP concentrations were found, and slopes were determined for linear relationships fitting the data for four different observation periods (fall, 1978; fall, 1979; spring, 1980; fall, 1980). The slope of FVC versus TSP was calculated for 335 children with three or more observations during any of the four study periods, with 194 having been tested during more than one study period. Individual regression coefficients for each child using pollution as the independent variable were calculated. The distribution of coefficients was then trimmed to eliminate outliers. Slopes for TSP using one

and five day averages were significantly lower than zero for both FVC and $FEV_{0.75}$. No overall dose-response relationship was estimated.

During November, 1984, Dassen et al. (1986) obtained baseline pulmonary function data for approximately 600 Dutch children aged 6 to 11. Then, a subset of the same children (N = 62) was retested in January, 1985, during an air pollution episode when 24-h mean values for TSP (hi-vol samples), RSP (respirable suspended particulate, cyclone sampler), and $S0_2$ (acidimetric technique) measured via a 6-station network all reached 200 to 250 $\mu g/m^3$. Lung function values of 62 children were taken at the end of the episode. Growth adjusted FVC values decreased by an average of 62 ml (11), $FEV_{1.0}$ values by 50 ml (10), and Peak Expiratory Flow Rate (PEFR) values by 219 ml/sec (62), all statistically significant decreases. Several lung function parameters showed statistically significant average declines of 3 to 5% at second (episode) testing compared to each child's own earlier baseline values, including decrements in both FVC and FEV levels on the second day of the episode, as well as for measures reflecting small airway functioning (i.e., maximum mid-expiratory flow and maximum flow at 50% vital capacity). Declines from their original baseline values for these parameters were still seen 16 days after the episode upon retesting of another subset of the children, but no differences were found between baseline and retest values for a third subset of children reevaluated 25 days after the episode. The 24-h mean TSP, RSP, and SO_2 levels measured in the 100 to 150 $\mu g/m^3$ range just prior to the last lung function tests may not have been sufficient to cause observable pulmonary function effects in children.

Quackenboss et al. (1991) reported results of a lung function study of asthmatic children aged 6 to 15 years in Tuscon, AZ. The data were collected over two week periods from May 1986 to November 1988. Peak flow rates (PEFR) were measured with mini-Wright peak flow meters with three tests during each of four time periods per day (morning, noon, evening, bed). Activity patterns were recorded in diaries, as well as symptoms and medication use. Measurements of $PM_{2.5}$, PM_{10}, and NO_2 were made both inside and outside the home during the two week period for 50% of the homes. $PM_{2.5}$ levels were elevated in homes with environmental tobacco smoke. Exposures for the remaining homes were estimated statistically. A random effects linear model was used to estimate the effect of pollutants and other covariates on PEFR. The NO_2 levels had the greatest effect on PEFR rates, but the indoor $PM_{2.5}$ levels were associated with a 15 ml/s decrease in morning PEFR (within day change) per unit increase of

$PM_{2.5}$ in $\mu g/m^3$. The relationships were unaffected by the inclusion of weather variables such as temperature, wind speed, and dew point.

Pope et al. (1991) studied pulmonary function (PEFR) in asthmatic school children in the Utah Valley. The group of participants was selected from 4th and 5th grade elementary students in 3 schools in the immediate vicinity of PM_{10} monitors operated by the Utah State Department of Health in Orem and Lindon, UT. PM_{10} values for 24-h samples collected from midnight to midnight ranged from 11 to 195 $\mu g/m^3$. There was limited monitoring of SO_2, NO_2, and O_3. Participants were restricted to those who responded positively to one of: ever wheezed without a cold, wheezed for 3 days out of a week for a month or longer or had a doctor say the "child has asthma". This resulted in 34 subjects being included in the final analyses. PEFR values were averaged across participants, and the deviations were analyzed using single period and polynomial-distributed lag models. The estimated coefficient for PM_{10} was -0.0110 l/min (0.0082). This coefficient corresponds to a 9.2 ml/s decrease in PEFR for a 50 $\mu g/m^3$ increase in PM_{10}. This effect was not statistically significant, but using a five day moving average of PM_{10} did result in a significant regression coefficient. The relationship was not affected by the inclusion of low temperature as a covariate.

Pope et al. (1991) also studied pulmonary function (PEFR) in asthmatics aged 8 to 72 in the Utah Valley, selected from those referred by local physicians. This resulted in 21 subjects being included in the final analysis. PM_{10} monitors operated by the Utah State Department of Health collected 24 h samples from midnight to midnight (PM_{10} range 11 to 195 $\mu g/m^3$). There was limited monitoring of SO_2, NO_2, and ozone. PEFR values were averaged across participants, and the deviations were analyzed using single period and polynomial-distributed lag models. The estimated coefficient for PM_{10} was -0.0175 l/min (0.0092), corresponding to a 14.6 ml/s decrease in PEFR for a PM_{10} 50 $\mu g/m^3$ increase. This effect was not statistically significant, but using a five day moving average of PM_{10} did result in a significant regression coefficient. The relationship was not affected by the inclusion of low temperature as a covariate.

Pope and Dockery (1992) also studied non-asthmatic symptomatic and asymptomatic Utah Valley children selected from 4th and 5th grade elementary students in the three schools near PM_{10} monitors in Orem and Lindon, UT. Of 129 children identified by questionnaire as being mildly symptomatic, 60 were selected; and 60 more with no symptoms were selected. The subjects were followed from December 1, 1990 to March 15, 1991. Utah State Department of

Health PM_{10} monitors collected 24 h samples from midnight to midnight; PM_{10} ranged from 7 to 251 $\mu g/m^3$. For purposes of analyses, five day moving averages of PM_{10} were used for exposure estimates. Limited monitoring of SO_2, NO_2, and O_3 was conducted. Mean deviations of PEF were computed for each individual. Weighted least squares regression found a minus 0.00060 (0.00020) change in PEF per $\mu g/m^3$ PM_{10} in symptomatic children and a minus 0.00042 (0.00017) change in PEF per $\mu g/m^3$ PM_{10} in asymptomatic children. No relationship between low temperature and PEF was found.

Koenig et al. (1993) studied two groups of elementary school children, one during the school year 1988 to 1989 and another during the school year 1989 to 1990. The subjects in the first study included 326 children, 24 of whom were asthmatics. During the second year, only 20 asthmatics were studied (14 of which were in the original study). The FVC and $FEV_{1.0}$ were measured for each child in September, December, February, and May of each year. Fine particles, considered to be the primary pollutant of interest, were measured by nephelometer, with 12-h averages (7:00 PM to 7:00 AM) being used as the exposure measure. Additional information on $PM_{2.5}$ was collected and shown to be linearly related to light scattering (r^2 = 0.945). A mixed model was used to analyze the data. The model included random effects terms for the individuals and fixed effects terms for height, temperature, and light scattering. No relationship was found between light scattering and lung function in the larger sample, but a significant relationship was found in the asthmatics. When converted to $PM_{2.5}$ units, the decrease in $FEV_{1.0}$ was minus 0.0017 (0.0006) liters/($\mu g/m^3$). Effects of other pollutants were not considered.

Silverman et al. (1992) studied 36 asthmatic children over a 10-day period in the summer and a 10-day period in the winter in Toronto, Canada. Subjects in the first study (17 subjects) and in the second (19 subjects) were selected from a pool of 800 asthmatic children from the Gage Research Institute in Toronto. Patients were selected if they had a diagnosis of asthma and experienced wheezing at least a few times a week. Lung function measurements were obtained at the start and end of each day. Subjects carried a portable monitor which measured PM, SO_2, and NO_2. The first study measured particles less then 25 microns, the second less than 10 microns. The regression coefficient of $FEV_{1.0}$ on PM was -0.78 ml/($\mu g/m^3$) for the summer and 0.18 ml/($\mu g/m^3$) for the winter for Study 1, and −1.65 and 2.83 ml/($\mu g/m^3$) for the summer and winter in Study 2. No standard errors were given. The SAS analysis procedure was not

specified, and there was no mention of a repeated measures design. Results were not reported for SO_2 and NO_2 as exposure variables.

Hoek and Brunekreef (1993) studied pulmonary function in 112 children aged 7 to 12 residing in a non-urban area near Wageningen, NL. Spirometry was performed every three weeks for a total of six times; and one more measurement was made during an air pollution episode. PM_{10} was measured daily (3PM to 3PM) with an instrument similar to the Sierra Anderson 241 dichotomous sampler. SO_2 was measured by fluorescence and NO_2 by chemiluminescence. Linear regression analysis using the SAS procedure AUTOREG yielded an estimated coefficient for FEV_1 with PM_{10} of -0.55 ml/($\mu g/m^3$) (0.10) and for PEF of -0.82 (ml/s)/($\mu g/m^3$) (0.50). Lagged PM_{10} values gave similar coefficients. SO_2 and black smoke coefficients were similar in magnitude. Thus, both FEV_1 and PEF showed decreases related to pollution measures, but it was not possible to seperate out effects of one or another pollutant.

Hoek and Brunekreef (1994) studied pulmonary function and respiratory symptoms in Dutch children aged 7 to 11 in the towns of Deurne, Enkhuizen, Venlo, and Nijmegen, NL. Each child was studied six to ten times during one of three winters (1987/88, 1988/89, 1989/90). Measurements of FEV were obtained along with information on respiratory symptoms. PM_{10} was measured daily (3 pm to 3 pm), as were SO_2 and NO_2. Linear regression analysis using the SAS procedure MODEL with the %AR macro was used. The estimated coefficient for FEV_1 with PM_{10} was -0.10 ml/($\mu g/m^3$) (0.06) and the estimated coefficient for PEF was −0.82 (ml/s)/($\mu g/m^3$) (0.29). Lagged PM_{10} values gave similar coefficients. PM_{10} and NO_2 coefficients remained significant after adjusting for ambient temperature, but pollutants such as SO_2, HONO, sulfate and nitrate did not. Other adjustments for factors such as relative humidity, self-reported colds, and learning effects did not affect magnitudes of estimated coefficients.

Lebowitz et al. (1992) studied 30 children with a current diagnosis of asthma using PEFR measurements twice daily. A total of 674 PEFR measurements were analyzed, and information on individual activity patterns was collected. $PM_{2.5}$ and PM_{10} samples were collected in 50% of the homes. Six local monitoring stations were used to measure outdoor exposure. Using a random effects model, PEFR was found to be significantly lower in the morning for children who lived in homes with higher PM concentrations.

Johnson et al. (1982) studied lung function in children as part of the Montana Air Pollution Study, designed to collect sequential pulmonary function data on children from November 1979

to April 1980 at six different time points. By adding a 7th round of testing on May 23, 1980, the study took advantage of the natural experiment created by the eruption on May 18, 1980 of the Mt. St. Helens volcano in Washington state. About 100 children had been measured for FVC, $FEV_{1.0}$, and FEF_{25-75} on six earlier occasions. During five of these measurement periods the 3-day TSP average was relatively low (98 to 154 $\mu g/m^3$), but in one period, the average was 440 $\mu g/m^3$. The eruption of the volcano on May 18, 1980 forced nearly everybody indoors for the following three days. Most children who ventured out did so with masks on. By May 23, the air had cleared enough so that children returned to school, and their pulmonary function was measured. The TSP values for the four preceding days ranged from 948 to 11,054 $\mu g/m^3$. The authors used an unusual method of analysis, described in the appendix of their report. Interestingly, there was a larger decrease in lung function on the 400 $\mu g/m^3$ day than there was on the day following the high volcanic ash episode.

Johnson et al. (1990) studied pulmonary function in 120 3rd and 4th grade children in Missoula, MT during 1978 to 1979 who were tested up to six times between October 1978 and May 1979. FVC, $FEV_{1.0}$, and FEF_{25-75} were measured. TSP was monitored daily near the center of the study area. RSP was measured every third day and estimated from TSP and other variables on the other days. The average of the current day's and the previous two day's pollution was used as the estimate of exposure. Each child who had at least three readings was used as his own control. Percent changes in FVC, $FEV_{1.0}$, and FEF_{25-75} on higher pollution days as compared with the same measurements on days with lower pollution exposure were used as the response variable. FVC averages were decreased about 0.40% on days with RSP 31 to 60 $\mu g/m^3$ and decreased about 0.75% on days with RSP > 60 $\mu g/m^3$. Similar but smaller changes were seen in $FEV_{1.0}$ and FEF_{25-75}. All changes were marginally significant. No other pollutants were mentioned.

Roemer et al. (1993) studied Dutch children with chronic respiratory symptoms. Parents of children in grades 3 to 8 in two small nonindustrial towns in the Netherlands were given questionnaires about respiratory symptoms. Of the 313 children with positive responses for cough or shortness of breath (S.O.B), 74 were included in the study. Peak flows were measured in the morning and evening. PM_{10} was measured daily using an Anderson dichotomous sampler. Black smoke (BS), SO_2, and NO_2 were also measured. Regression coefficients for both morning and evening current day's PM_{10} levels were significant, but lagged PM_{10} values were not. The

coefficient for current day's PM_{10} with morning PEF was -0.90 (ml/s)/($\mu g/m^3$) (0.28). Evening peak flow, but not morning peak flow, was also significantly related to SO_2; BS, however, was not related to peak flow.

Studnicka et al. (1995) studied acidic particles in a summer camp study in southern Austria between June 28 and August 28, 1991. Daily spirometry was measured in three panels of children age 7 or older, for a total of 133 subjects. On site measurements were taken for PM_{10}, H^+, sulfate, ammonia, and ozone. A repeated measures linear regression model was fitted using a SAS macro. Pulmonary function measurements made by a rolling-seal-type instrument (which gave flow-volume tracings) yielded $FEV_{1.0}$, FVC, and PEFR data. The results from all three panels combined suggested that PM_{10} was marginally related to a decrease in $FEV_{1.0}$, but was less related to FVC and PEFR. Results for H^+ are discussed in Section 12.5. The coefficient for FVC suggested that an increase of 50 $\mu g/m^3$ in PM_{10} was associated with a 66 ml (39) decrease in FVC and a 99 ml/s (99) decrease in PEFR.

Neas et al. (1995) studied peak expiratory flow rates in 83 children in Uniontown, PA. PEFR rates were measured over an 87 day period during summer 1990, using a Collins recording survey spirometer. Air pollution data was collected from a monitoring site located 2 km north of the center of the town, and included PM_{10}, $PM_{2.5}$, ozone, SO_2, sulfate fraction, and H^+. The $PM_{2.5}$ values had a mean of 24.5 $\mu g/m^3$ and an interquartile range of 18.9. The PEFR values were analyzed using the autoregressive integrated moving average procedure of SAS. The model included terms for temperature, time trend, and second-order autocorrelations. The largest decreases in PEFR were related to H^+, but they were also related to both $PM_{2.5}$ and ozone.

Studies of Pulmonary Function in Adults

Pope and Kanner (1993) studied adults in the Salt Lake Valley, using spirometric data from the NHLBI-sponsored Salt Lake City Center of the Lung Health Study. Based on presence of mild COPD and willingness to participate in a 5-year smoking cessation study, 624 participants were selected. Analyses were based on two initial screening visits before randomization into the NHLBI Study; 399 subjects had adequate data to be in the analyses. PM_{10} monitors operated by the Utah State Department of Health collected 24-h samples

midnight to midnight. Limited monitoring of SO_2, NO_2, and O_3 showed these pollutants to always be well below their respective NAAQS, and none were included in the analyses. Regression analyses for change in FEV_1 (liters) per change in PM_{10} ($\mu g/m^3$) found a coefficient of -0.58 ml/($\mu g/m^3$). Changes were also seen in the ratio of FEV_1 to FVC, but PEF was not measured.

Dusseldorp et al. (1994) studied pulmonary function in 32 adults living near a large steel plant in Wijk aan Zee, NL. During the study period, PM_{10} levels ranged from 36 to 137 $\mu g/m^3$. Peak flow measurements (PEFR) were measured twice daily using a Mini Wright peak flow meter. Diary information on acute respiratory symptoms, medication use, and presence of fever was also collected. The study was conducted from 11 October 1993 to 22 December 1993, and the average number of days per subject was 66. Multiple linear regression analysis with adjustment for first order autocorrelation. The regression coefficient for evening PEFR on PM_{10} (lag zero) was -0.90 (ml/s)/$\mu g/m^3$ (0.36), and for morning PEFR on PM_{10} (lag zero) it was -1.53 (ml/s)/$\mu g/m^3$ (0.43). These correspond to estimated decreases in PEFR per 50$\mu g/m^3$ PM_{10} increase of 45 and 77 ml/sec respectively. Lags of one, two, and three days were also fitted, but gave smaller estimated coefficients.

Perry et al. (1983) conducted a longitudinal study of 24 Denver area asthmatics' pulmonary function, symptoms, and medication use followed daily January through March, 1979. Peak flows (from Mini-Wright Peak Flow Meters), symptoms, and medication use were measured twice a day. Fine and coarse PM mass (as well as sulfate and nitrate fractions) were available from an east and a west Denver site, and CO, SO_2, and O_3 were all also measured. Dichotomous, virtual impactor samplers provided daily measurements of thoracic PM (total mass, sulfates, and nitrates), for coarse (2.5 to 15 μm) and for fine fractions (<2.5 μm), with all PM measures being relatively low during the study.

Temperature and barometric pressure were also measured. Individual subject data were analyzed separately by regression analysis. The coefficients were then tested using a non-parametric Wilcoxon signed rank test. None of the PM measures were associated with changes in any of the health endpoints. This study had very low power, given the small sample size and lack of high PM levels.

Acute Pulmonary Function Studies Summary

Pulmonary function results are slightly easier to compare because most studies used peak flow (PEFR) or forced expiratory volume (FEV) as the health end-point measure. The acute pulmonary function studies (summarized in Table 12-13) are suggestive of a short term effect resulting from PM pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 µg/m^3 in PM_{10} or its equivalent (see Figure 12-6). The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using FEV_1 or FVC as endpoints are less consistent. For comparison, a study of over 16,000 children found that maternal smoking decreased a child's FEV by 10 to 30 ml (Hasselblad et al., 1981).

Pope and Kanner (1993) provided one estimate of the effect of PM on pulmonary function in adults. They found a 29 (±10) ml decrease in FEV_1 per 50 μg/m^3 increase in PM_{10}, which is similar in magnitude to the changes found in children. Dusseldorp et al. (1994), in comparison, found 45 and 77 ml/sec decreases for evening and morning PEFR, respectively, per 50 μg/m^3 increase in PM_{10}.